Jukka Montonen

Plant Foods in the Prevention of Type 2 Diabetes Mellitus with Emphasis on Dietary Fiber and Antioxidant Vitamins

Publications of the National Public Health Institute A 13/2005

National Public Health Institute,
Helsinki, Finland
and
Department of Public Health,
University of Helsinki, Finland

Jukka Montonen

PLANT FOODS IN THE PREVENTION OF TYPE 2 DIABETES MELLITUS WITH EMPHASIS ON DIETARY FIBER AND ANTIOXIDANT VITAMINS

ACADEMIC DISSERTATION

To be presented with the permission of the Faculty of Medicine, University of Helsinki, for public examination in Auditorium XII, University Main Building, on October 19, 2005, at 12 o'clock noon.

National Public Health Institute, Helsinki, Finland
and
Department of Public Health, University of Helsinki, Finland

Helsinki 2005

Publications of the National Public Health Institute
KTL A13 / 2005

Julkaisija-Utgivare-Publisher

Kansanterveyslaitos (KTL)
Mannerheimintie 166
00300 Helsinki
Puh. vaihde (09) 474 41, telefax (09) 4744 8408

Folkhälsoinstitutet
Mannerheimvägen 166
00300 Helsingfors
Tel. växel (09) 474 41, telefax (09) 4744 8408

National Public Health Institute
Mannerheimintie 166
FIN-00300 Helsinki, Finland
Telephone +358 9 474 41, telefax +358 9 4744 8408

ISBN 951-740-538-3
ISSN 0359-3584
ISBN 951-740-539-1 (pdf)
ISSN 1458-6290 (pdf)

Kannen kuva - cover graphic: Eero Lilja

Edita Prima Oy
Helsinki 2005

Supervised by

Research Professor Paul Knekt, PHD
National Public Health Institute,
Helsinki

and

Docent Ritva Järvinen, PhD
Department of Clinical Nutrition
University of Kuopio
Kuopio

Reviewed by

Professor Leena Räsänen, DSc
Division of Nutrition
Department of Applied Chemistry and Microbiology
University of Helsinki

and

Docent Leena Moilanen, MD, PhD
Department of Medicine
University of Kuopio

Opponent

Professor Matti Uusitupa, MD, PhD
University of Kuopio

Montonen Jukka, Plant foods in the prevention of type 2 diabetes mellitus with emphasis on dietary fiber and antioxidant vitamins.
Helsinki: Publications of the National Public Health Insitute, A13/2005, 150 pages
ISBN 951-740-538-3; 951-740-539-1 (pdf-version)
ISSN 0359-3584; 1458-6290 (pdf-version)
http://www.ktl.fi/portal/suomi/julkaisut/julkaisusarjat/kansanterveyslaitoksen_julkaisuja_a/

ABSTRACT

Incidence of type 2 diabetes is rising rapidly. Obesity and low levels of physical activity are the most potent modifiable risk factors for type 2 diabetes. In addition to these lifestyle factors, several hypotheses relating diet to the prevention of type 2 diabetes have been suggested. However, evidence on dietary factors in the prevention of type 2 diabetes is incomplete.

Plant foods were studied for their ability to predict incidence of type 2 diabetes mellitus. First, major dietary patterns were identified and a pattern characterized by consumption of fruit and vegetables was further studied for its predictive value on the incidence of type 2 diabetes. In more profound analyses of individual foods, the components of the identified dietary pattern were studied. Finally, the major biological hypotheses linking nutrients derived from plant foods to prevention of type 2 diabetes were tested.

The study population was derived from the population-based data from the Finnish Mobile Clinic Health Examination Survey. Food consumption of 10 054 participants during the previous year was estimated using a dietary history interview. A total of 4 304 men and women, 40–69 years of age and free of diabetes at baseline in 1967–1972 were followed up for diabetes incidence during a 23-year period. During the follow-up, a total of 383 incident cases occurred.

Two major dietary patterns were identified which were labeled as ‘prudent’ and ‘conservative’. The prudent pattern was characterized by higher consumption of fruits, berries and vegetables. The prudent dietary pattern was associated with a reduced risk of type 2 diabetes. Of the components of the prudent pattern, higher intakes of green vegetables, fruit and berries, oil and margarine predicted a reduced risk of type 2 diabetes. Results from further analyses also suggested that the relation between the prudent pattern and diabetes risk was completely explained by major components of the dietary pattern, suggesting that the pattern actually summarizes the effects of individual foods or food groups rather than carrying further information on food synergy. Whole grain consumption was associated with a reduced risk of type 2 diabetes during 10 years of follow-up, but not during a 23-year follow-up. Of specific nutrients, cereal fiber and dietary antioxidant vitamins, such as vitamin E and carotenoids were associated with a reduced risk of type 2 diabetes, but vitamin C was not.

It seems conceivable that prevention of type 2 diabetes can be aided by the consumption of plant foods, which are rich in nutrients with hypothesized benefits in preventing diabetes. Accordingly, intakes of cereal fiber and antioxidant vitamins predicted reduced risk of type 2 diabetes mellitus. However, more studies are needed to clarify whether the inverse association between plant food consumption and type 2 diabetes is mediated by the hypothesized nutrients or other dietary components from plant foods or by lifestyle and sociodemographic factors related to the dietary pattern.

Keywords: Diabetes mellitus, epidemiology, diet, fruits, grains, prospective studies, vegetables

Montonen Jukka, Kasviperäinen ruoka aikuistyypin diabeteksen ehkäisyssä
– mielenkiinnon kohteena ravintokuitu ja antioxidanttivitamiinit.
Helsinki: Kansanterveyslaitoksen julkaisuja, A13/2005, 150 sivua
ISBN 951-740-538-3; 951-740-539-1 (pdf-versio)
ISSN 0359-3584; 1458-6290 (pdf-versio)
http://www.ktl.fi/portal/suomi/julkaisut/julkaisusarjat/kansanterveyslaitoksen_julkaisuja_a/

TIIVISTELMÄ

Aikuistyypin diabeteksen ilmaantuvuus kasvaa voimakkaasti väestössämme. Merkittävimmät elintapatekijät aikuistyypin diabeteksen synnyssä ovat lihavuus ja liikunnan puute. Näiden elintapatekijöiden lisäksi diabeteksen kehittymiseen on liitetty joukko ravintoon liittyviä hypoteeseja. Kuitenkin näyttö ravintotekijöiden merkityksestä aikuistyypin diabeteksen kehittymisessä on vielä puutteellista.

Tässä tutkimuksessa selvitettiin kasviperäisen ravinnon yhteyttä aikuistyypin diabeteksen ilmaantuvuuteen. Tutkittavien ruoankäyttötiedoista tunnistettiin pääruokavaliotyypit, jonka jälkeen tutkittiin hedelmiä ja kasviksia sisältävän ruokavaliotyypin yhteyttä aikuistyypin diabeteksen ilmaantuvuuteen. Edelleen tutkittiin yksittäisten kasvikunnasta peräisin olevien ruoka-aineiden käytön yhteyttä diabeteksen riskiin ja lopulta testattiin keskeisiä biologisia hypoteeseja kasvikunnasta saatavien ravintoaineiden saannin yhteydestä aikuistyypin diabeteksen ilmaantuvuuteen.

Tutkimusaineistona käytettiin Kansaneläkelaitoksen autoklinikkatutkimuksessa tehdyn ravintotutkimuksen ruoankäyttötietoja. Kaikkiaan 10 054 henkilön ruoankäyttö mitattiin edellisen vuoden kattavalla ruoankäyttöhaastattelulla. Tämä tutkimus pohjautuu 4 304:een 40–69 vuotiaaseen henkilöön, joilla ei ollut diabetesta, kun ruoankäyttöaineisto kerättiin vuosina 1967–1972. Kansaneläkelaitoksen ilmaislääkerekisteristä tunnistettiin 383 diabetekseen sairastunutta tutkittavien henkilötunnusten avulla 23 vuoden seurannan aikana.

Tutkimuksessa tunnistettiin kaksi ruokavaliotyyppiä. jotka nimettiin järkeväksi ”pruden dietary pattern” sekä perinteiseksi ”conservative dietary pattern” ruokavalioksi. Järkeväksi nimetty ruokavaliotyyppi liittyi runsaaseen kasvisten, hedelmien sekä marjojen käyttöön. Tämä järkevä ruokavaliotyyppi ennusti pienentynyttä vaaraa sairastua aikuistyypin diabetekseen. Kasviperäisistä ruoka-aineista vihreiden kasvisten, hedelmien ja marjojen, ruokaöljyn sekä margariinin käytön havaittiin olevan käänteisessä yhteydessä aikuistyypin diabeteksen riskiin. Jatkoanalyyseissä ilmeni, että järkevän ruokavaliotyypin yhteys diabeteksen riskiin selittyi kasvisten, hedelmien ja marjojen sekä öljyn ja margariinien käytöllä. Tulos

viittaa siihen, että ruokavaliotyyppi kuvaa sisältämiensä ruoka-aineiden summaa, mutta näyttäisi siltä, ettei se sisällä informaatiota ruoka-aineiden potentiaalisesta synergistisestä vaikutuksesta. Tutkimuksessa havaittiin kokojyväviljan saannin olevan käänteisessä yhteydessä aikuistyypin diabeteksen riskiin, kun seuranta-aika rajattiin 10 vuoteen, mutta ei seurannan ollessa 23 vuotta. Edelleen havaittiin, että viljakuidun, E-vitamiinin sekä karotenoidien saannit olivat käänteisessä yhteydessä aikuistyypin diabeteksen ilmaantuvuuteen, mutta C-vitamiinin saannilla ei yhteyttä todettu.

Tämä tutkimuksen tulokset viittaavat siihen, että aikuistyypin diabeteksen kehittymistä voidaan hillitä käyttämällä kasvikunnasta peräisin olevia ruoka-aineita, erityisesti vihreitä kasviksia, hedelmiä ja marjoja, ruokaöljyä sekä margariinia. Tämä tutkimus vahvistaa hypoteesia viljakuidun sekä antioksidanttivitamiinien diabetesta ehkäisevästä vaikutuksesta. Kuitenkin lisää tutkimuksia tarvitaan sen selvittämiseksi johtuuko käänteinen yhteys kasvikunnasta peräisin olevan ruoan ja diabeteksen riskin välillä hypoteesin mukaisten ravintoaineiden, vai muiden kasvikunnasta saatavien ravintoaineiden saannista vai kasvikunnan tuotteiden käyttöön liittyvistä muista elintapatekijöistä.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in the text by their Roman numerals:

I Montonen J, Knekt P, Härkänen T, Järvinen R, Heliövaara M, Aromaa A, Reunanen A. Dietary patterns and the incidence of type 2 diabetes. Am J Epidemiol. 2005;161: 219-227.

II Montonen J, Järvinen R, Heliövaara M, Reunanen A, Aromaa A, Knekt P. Food consumption and the incidence of type II diabetes mellitus. Eur J Clin Nutr. 2005;59:441-448.

III Montonen J, Knekt P, Järvinen R, Aromaa A, Reunanen A. Whole-grain and fiber intake and the incidence of type 2 diabetes. Am J Clin Nutr. 2003;77:622-629.

IV Montonen J, Knekt P, Järvinen R, Reunanen A. Dietary antioxidant intake and risk of type 2 diabetes. Diabetes Care. 2004;27:362-366.

These articles are reproduced with the kind permission of their copyright holders.

1 INTRODUCTION

The population in Finland is aging and the incidence of type 2 diabetes is rising rapidly in the older age groups (Niemi and Winell 2005). An increased incidence has also been noted even among children (Alberti et al. 2004). The total number of Finnish people with diabetes has been approximated at 200 000 and a majority (about 80%) of these people have type 2 diabetes (Reunanen 2004). Consequently, medical treatment of the increasing number of patients with type 2 diabetes will add to the health care burden. The annual costs of health care for persons with diabetes are over 11 percent of the total annual costs for health care in Finland (Kangas 2002). Most of the costs arising from the treatment of diabetes are due to the treatment of complications. Studies focusing on preventing the development of diabetes are therefore highly welcome as they ease the developing burden.

Obesity and low levels of physical activity are the most potent modifiable risk factors for type 2 diabetes. Accordingly, modification of lifestyle to increase physical activity and achieve moderate weight loss has been shown to prevent the development of diabetes (Pan et al. 1997; Tuomilehto et al. 2001; Knowler et al. 2002). In addition to these life-style modifications, several hypotheses relating diet to the prevention of type 2 diabetes have been suggested. Plant foods such as fruits and vegetables, grains, nuts and legumes have been thought to assist in the prevention of type 2 diabetes due to their richness in fiber, antioxidant vitamins and other bioactive components and lower glycemic index (Slavin et al.1999; Prior 2003). Despite the hypotheses relating diet to the development of type 2 diabetes, there are few comprehensive studies on the association between intakes of individual plant foods and diabetes risk.

Research strategies that start with foods or food patterns, and then take these larger units apart to isolate simpler pathways are termed “top-down strategy” (Jacobs and Steffen 2003). It has been suggested that instead of the single-nutrient approach more emphasis should be paid to “top-down” strategies to reveal potential food synergies (Jacobs and Murtaugh 2000). To study food synergies the dietary pattern approach has become a tool for automatically including the interactions between potentially effective nutrients in the effect estimate. On the other hand, it is still an open question whether interactions between nutrients, rather than a simple sum of the effect of individual components, contribute to the predictive value in the dietary pattern approach.

The impact of dietary factors on the incidence of type 2 diabetes can only be studied in large prospective population studies with proper information on diet at baseline. The Finnish Mobile Clinic Health Examination Survey was excellently suited for the purpose. This large nationwide cohort of Finns includes dietary data collected using a one-year dietary history method and reliable register data on the occurrence of diabetes. In the present follow-up study, the relationships between plant foods and diabetes incidence were investigated using a “top down approach” (Jacobs and Steffen 2003). First, the major dietary patterns were identified and studied for their association with type 2 diabetes incidence. Thereafter, the prediction of components of the plant food rich pattern were investigated in relation to diabetes risk, and finally the major hypotheses on nutrients from plant foods and diabetes were studied in order to establish their potential in predicting type 2 diabetes.

2 REVIEW OF THE LITERATURE

2.1 Type 2 diabetes

2.1.1 Definition and diagnosis

Diabetes is a group of diseases characterized by elevated blood glucose concentration. Diabetes may be a consequence of either diminished or totally exhausted insulin secretion from pancreatic β-cells, weakened glucose uptake (insulin resistance), or both (WHO 1999). Normally properly treated diabetes is symptomless, but continuing hyperglycemia in diabetes may cause retinopathy, neuropathy and nephropathy (Vinik et al. 2003), and macro vascular complications (Pyörälä et al. 1987), which have been related to premature mortality and morbidity (Uusitupa et al. 1993).

Diabetes can be classified in two major classes: type 1 diabetes (juvenile-onset diabetes, insulin dependent diabetes), and type 2 diabetes (adult-onset diabetes, non-insulin dependent diabetes). Type 1 diabetes is characterized by total exhaustion of insulin secretion and type 2 diabetes is mainly characterized by insulin resistance, but impairment in insulin secretion also occurs in type 2 diabetes (Weyer et al. 1999; Lebovitz 2001). In addition to these main classes, other sub-classes are latent autoimmune diabetes in adults (LADA) (Tuomi et al. 1999; Pozzilli and Di Mario 2001) and maturity-onset diabetes of the young (MODY) (Owen and Hattersley 2001).

The diagnostics of type 2 diabetes is based on the measured blood glucose level. However, the fundamental question is whether a threshold level exists for the occurrence of later complications. The diagnostic criterion for fasting plasma glucose values has been established on the basis of several population-based studies on the incidence of complications. In the present study, the diagnostic criteria for diabetes were based on the criteria defined by the World Health Organization (WHO) in 1985 (WHO 1985). According to these criteria, a fasting venous plasma glucose concentration of less than 6.4 mmol/l and a 2-h value in oral glucose test of less than 7.8 mmol/l is considered normal. A fasting plasma glucose concentration of less than 7.8 mmol/l and a two-hour glucose tolerance test value of between 7.8 mmol/l and 11.0 mmol/l refers to impaired glucose tolerance. Diabetes is diagnosed when the fasting plasma glucose concentration is 7.8 mmol/l or more and the two-hour oral glucose tolerance test value is 11.1 mmol/l or more (WHO 1985). Diagnostic criteria for diabetes were revised in 1999 (WHO 1999). The criterion for normal plasma glucose level was decreased to 6.1 mmol/l or less and the criterion for fasting plasma glucose to indicate diabetes was decreased to 7.0 mmol/l. According to these new criteria, a fasting plasma glucose concentration of less than 7.0 mmol/l, but two-hour glucose tolerance test values of between 7.8 mmol/l and 11.1 mmol/l indicate impaired glucose tolerance. A new state, impaired fasting glucose, was introduced which refers to a state when fasting glucose is slightly increased (6.1 – 6.9 mmol/l) and the two-hour glucose tolerance test value is less than 7.8 mmol/l (WHO 1999).

For research purposes, measurements of fasting insulin levels may be used as a measure of insulin resistance due to good correlation with insulin sensitivity (Laakso 1993). For epidemiological studies of glucose metabolism, fasting blood glucose may be used due to its high correlation with the 2-h values of the oral glucose tolerance test (WHO 1999). The concept of syndrome X, also called metabolic syndrome or insulin resistance syndrome, was introduced in 1988 (Reaven 1988). The metabolic syndrome is a multifaceted syndrome characterized by abnormalities such as obesity, hypertension, insulin resistance, glucose intolerance and dyslipidaemia and it is highly predictive of type 2 diabetes (Grundy et al. 2004). Glycated hemoglobin (HbA_{1C}) is a marker of long-term glucose control (Ashby et al. 1985), although the measured values vary not only according to the level of glycemia but also to the hemoglobin turnover rate of (Kuzuya et al. 2001). Besides fasting insulin concentrations, glucose and glycated hemoglobin, measurement of urine glucose has been used as a manifestation of type 2 diabetes (Goldstein et al. 2004).

2.1.2 Pathofysiology

In type 2 diabetes, two impairments are found to increase blood glucose levels: impaired insulin action and impaired pancreatic insulin secretion. Insulin resistance is defined as the inability of insulin to increase glucose uptake and utilization in an individual as much as in the normal population (Lebovitz 2001). When the target tissue does not respond to even high levels of insulin, glucose builds up in the blood resulting in high blood glucose or type 2 diabetes.

Insulin secretion from pancreatic β-cells in the islets of Lagerhans is mainly regulated by glucose entry via its transporter. The ability to secrete adequate amounts of insulin is determined by the functional integrity of β-cells and their overall mass (Klöppel et al. 1985; Kahn 1998). In response to elevated blood glucose concentration due to insulin resistance, β-cells need to increase the insulin secretion to maintain homeostasis in glucose levels. Finally, β-cells become unresponsive to glucose and eventually type 2 diabetes develops. Normal insulin secretion from pancreatic β-cells is two-phased. In the first phase, the secretion is abundant and rapid to compensate for an acute postprandial glucose peak, whereas the second phase insulin release rises more gradually (Ward et al. 1984). In persons with type 2 diabetes, the first phase secretion that prevents postprandial hyperglycemia is missing or considerably weakened (Brunzell et al. 1976; Ward et al. 1984). The subsequent hyperglycaemia is deleterious to pancreatic β-cells and insulin secretion decreases further causing a vicious circle: the higher the blood glucose, the weaker the insulin secretion, while weakened insulin secretion increases the blood glucose level.

The liver has a key role in adjusting blood glucose levels. During fasting, the glucose neo-genesis from lactate and glycerol in the liver maintains the normal glucose level. Normally, the postprandial increase in glucose and insulin levels inhibits this hepatic gluconeogenesis (Hue 1987; Zubay 1995). In type 2 diabetes gluconeogenesis from glycerol is disproportionally increased contributing to fasting hypeglycaemia (Nurjhan et al. 1992; Puhakainen et al. 1992; Gelding et al. 1995).

2.1.3 Epidemiology

According to the national register of drug re-imbursements, 150 000 persons (approximately 3% of the population) were eligible for drug reimbursements for the treatment of diabetes in Finland in 2003 (Social Insurance Institution 2003). Prevalence of diabetes has increased substantially in Finland during the last quarter of the 20^{th} century, since the number of persons eligible for drug reimbursements for the treatment of diabetes was only 42 000 in the late seventies (Reunanen 2003). The register of drug re-imbursements does not give the number of persons with diet therapy only and consequently, the number of persons with diabetes is underestimated. A study project that combined different registers estimated the total number of Finns with type 2 diabetes to be approximately 200 000 (Niemi and Winell 2005). In the nationally representative Health 2000 Survey among persons aged over 30, four percent of the men and three percent of the women had type 2 diabetes according to a physician's clinical examination (Reunanen et al. 2004). The prevalence increases sharply with age. Accordingly, the proportion of persons with type 2 diabetes was 9% among those aged over 65. Type 2 is the predominant type of diabetes in Finland. In the Health 2000 Survey only 0.7% of the men and 0.3% of the women had type 1 diabetes (Reunanen et al. 2004).

The increasing prevalence of type 2 diabetes is a global health problem and closely related to the increasing prevalence of obesity due to western lifestyles (Songer and Zimmet 1995). Amos et al. (1997) estimated that there was 124 million persons with diabetes in the world in 1997 and predicted this number would grow to 221 million in 2010. Another study group estimated that the number of persons with diabetes was 150 million in 2000 and this number is expected to double by 2025

(King et al. 1998). The largest increase in the prevalence numbers is thought likely to appear in India, China and other developing countries.

2.1.4 Major risk factors

The risk of type 2 diabetes increases with age (Narayan et al. 2003). Obesity is another risk factor in the development of diabetes (McPhillips et al. 1990; Ferrannini et al. 1997; Wei et al. 1997). According to several case-control studies 60–80% of persons with type 2 diabetes have been obese (Virtanen and Aro1994). A third major risk factor is physical inactivity. Physical activity has been consistently related with decreased risk of type 2 diabetes in observational studies (Manson et al. 1991; Manson et al. 1992; Perry et al. 1995; Lynch et al. 1996; Hu et al. 1999a; Folsom et al. 2000; Hu et al. 2001a) and experimental studies have shown the beneficial effects of physical exercise on insulin sensitivity (Burstein et al. 1990; Eriksson et al. 1997; Duncan et al. 2003). The effect of physical inactivity is partly mediated by weight gain, but it has been shown that insulin sensitivity can be improved by physical training independent of the level of obesity.

Other relevant risk factors are family history of diabetes (Knowler et al. 1981; Jarrett et al. 1989), low birth weight (Hales et al. 1991; Barker et al. 1993; Rich-Edwards 1999; Forsén et al. 2000), gestational diabetes (Metzger et al. 1993), high blood pressure (Skarfors 1991; Stolk et al. 1993), smoking (Rimm et al. 1993; Rimm et al. 1995; Mikhailidis et al. 1998), abundant alcohol consumption (Rimm et al. 1995; Perry et al.1995; Wannamethee et al. 2003) and unsatisfactory dietary patterns (van Dam et al. 2002a). Most of the dietary risk factors are related to western diets: abundant consumption of processed meat products, high energy intake, higher intake of saturated fat, and low fiber intake (Virtanen and Aro 1994; van Dam 2003). Dietary factors, physical activity and other life-style-related behavior are modifiable and therefore provide important avenues for actions targeted at prevention of type 2 diabetes.

2.2 Biological hypotheses linking plant foods in the prevention of type 2 diabetes

Plant foods, the foods derived from plant sources, such as vegetables, fruits, grains, legumes and nuts are generally recommended to be included in the diet mostly to prevent the development of chronic diseases (National Nutrition Council 1999; Franz et al. 2002). These plant foods are rich sources of nutrients that are hypothesized to prevent development of type 2 diabetes such as fiber, antioxidant vitamins, minerals, unsaturated fatty acids, folic acid, phytoestrogens and phenolic compounds (Prior 2003; Slavin 2004). Another important factor thought to mediate the effect of plant foods is reduction of the glycaemic index in mixed meals (Jenkins 1988). Besides the nutrients, studies have shown that postprandial glucose responses can be affected by the structure of food (Bjorck et al. 1994; Granfeld et al. 1995; Juntunen et al. 2003a). After all, plant foods are usually rather satiating foods and the preventive effect can be mediated by lower energy intake.

2.2.1 Dietary fiber and digestion and absorption of carbohydrates

The development of diabetes has been suggested to be related to scarcity of fiber in the diet (Trowell 1978). Two biological mechanisms have been hypothesized as mediating the effect of fiber in preventing the development of type 2 diabetes (Trowell 1975; Anderson et al. 1979). The beneficial effect of soluble fiber may be mediated through slow absorption and digestion of carbohydrates leading to a reduced insulin demand (Jenkins et al. 1977; Spiller et al. 1980; Würsch and Pi-Sunyer 1997; Slavin et al. 1999). Insoluble fiber shortens the intestinal transit time, which therefore allows less time for carbohydrates to be absorbed (Kay et al. 1978; Anderson et al. 1979; Marlett et al. 2002). Experimental studies have shown that when carbohydrates are ingested with plant fiber, the subsequent rise in blood glucose is significantly lower than when the carbohydrate load is taken without fiber (Haber et al. 1977; Jenkins et al. 1977).

The glycemic index is a ranking of carbohydrates based on their immediate effect on blood glucose levels (Foster-Powell et al. 2002). Carbohydrates that break down quickly during digestion have the highest glycemic indices and the blood glucose response is fast and high. Carbohydrates that break down slowly, releasing glucose gradually into the blood stream, have a low glycemic index providing smaller stress on insulin secretion. The glycemic load is a product of the glycemic index value of a food and its carbohydrate content and it is used to represent the quality and quantity of the carbohydrates consumed (Salmeron 1997a; Salmeron 1997b). In general, unprocessed plant foods have a low glycemic index and glycemic load, which is one mechanism that may provide the potential preventive effect of plant foods in the development of diabetes. However, one should keep in mind that, besides the quality and quantity of the carbohydrates, the blood glucose response may also be influenced by other factors than carbohydrates in meals consisting of mixed foods.

2.2.2 Antioxidant theory

Free radicals are molecules with one or more unpaired electron. A moderate amount of these free radicals are formed endogenously as a result of physiological metabolic reactions. Formation of free radicals can be stimulated by exposure to UV light, by irradiation or chemically (Halliwell and Gutteridge 1989). Important exogenous sources of free radicals are tobacco smoke and diet. Formation of free radicals may also be a consequence of hyperglycemia (Brownlee 2001). The chronic oxidative stress caused by reactive oxygen species has been implicated in the development of diabetes (Oberley 1988; Rösen et al. 2001). Free radicals contribute to the destruction of pancreatic β-cells (Oberley 1988) and insulin resistance (Paolisso and Giugliano 1996; Rudich et al. 1997; Ceriello 2000; Maddux et al. 2001). These radicals oxidate phospholipids on cell membranes (Gordon 1996) and subsequent changes in the cell membrane may lead to impaired glucose intake of the cell. Increased lipid peroxidation in persons with type 2 diabetes has been found in human studies (Sato et al.1979; Kaji et al. 1985; Uzel et al. 1987).

An antioxidant is a compound able to donate an electron or a hydrogen atom to a free radical compound, without becoming itself an effective oxidant (Halliwell and Gutteridge 1989). It is a compound that protects biological systems against harmful effects of processes and reactions that can cause excessive oxidations (Krinsky 1992). Antioxidants have been shown to prevent the destruction of β-cells (Slonim et al.1983; Mutrhy et al. 1992) by inhibiting the peroxidation chain reaction and thus they may provide protection against the development of diabetes (Halliwell and Gutteridge 1989; Gordon 1996). In experimental studies in humans, pharmaceutical doses of tocopherol have been shown to reduce indicators of oxidative stress (Kähler et al. 1993), protein glycosylation (Ceriello et al. 1991), and improve insulin mediated glucose disposal (Paolisso et al. 1993a; Paolisso et al. 1994a; Paolisso et al. 1995) and glucose metabolism in persons with type 2 diabetes (Paolisso et al. 1993b). Since dietary antioxidants from fruits and vegetables are related to antioxidants available in circulation (Block et al. 2001; John et al. 2002), it appears conceivable that oxidative stress may be inhibited by eating plant foods. Vitamin C, vitamin E and carotenoids are the antioxidant vitamins provided by plant foods. Plant foods are also a good source of flavonoids and phenolic compounds that also have a potential preventive effect against development of diabetes due to their antioxidative nature (Prior 2003).

2.2.3 Alternative hypotheses on plant foods and diabetes development

Minerals, such as magnesium, potassium, chromium and zinc may affect glucose metabolism and insulin action. Deficiencies in these minerals have been implicated in the development of diabetes (Helderman et al. 1983; Singh et al. 1998; Anderson 2000; Gums 2004). Magnesium is a cofactor of several enzymes involved in phosphorylation reactions in carbohydrate metabolism and diminished levels of magnesium may reduce tyrosine kinase activity at insulin receptors (Suarez et al. 1995). Zinc has been found to affect the components of the insulin intracellular pathway (Tang and Shay 2001). Hypokalemia reduces the capacity of the pancreas to secrete insulin and therefore is a recognized reversible cause of glucose intolerance (Helderman et al. 1983). Chromium potentiates insulin action, but the specific biochemical function has not been clearly defined. It is thought that chromium potentiates insulin action through a direct action on insulin, its receptor or by regulating the synthesis of a molecule that potentiates insulin action (Nielsen 1994).

High fat intake probably contributes to the development of diabetes via obesity, but dietary fatty acids may have an effect on insulin resistance independent of obesity (Hu et al.2001c). It has been postulated that the mechanism is related to the fatty acid composition of the cell membranes (Pan et al. 1995; Vessby 2000). A high proportion of saturated fatty acids in the cell membrane could influence insulin action through changes in permeability and cell signaling and altering insulin receptor binding ability or affinity (Vessby 2000).

The biological mechanisms by which phytoestrogens may exert their beneficial effect on diabetes are not yet well known (Bhathena and Velasquez 2002). Some of the cellular and metabolic effects of isoflavones and lignans on diabetes may be mediated through estrogen receptor mediated mechanisms. Phytoestrogens are similar to estrogens in molecular structure and exert weakly estrogenic action (Adlercreutz & Mazur 1997). A non-estrogen receptor dependent mechanism in diabetes development may be mediated by inhibiting the activity of several enzymes, which are involved in cell-signaling mechanisms and nuclear events such as cell proliferation and differentiation (Akiyama et al. 1987; Okura et al. 1988; Markovits et al.1989; Linassier et al. 1990). Several lines of evidence suggest that phytoestrogens may favorably affect glucose homeostasis, insulin secretion, and lipid metabolism (Bhathena and Velasquez 2002). Animal studies have demonstrated that soy isoflavones improve glycemic control, lower insulin requirement, and increase insulin sensitivity (Vahouny et al, 1985; Iritani et al, 1997; Wagner et al, 1997; Lavigne et al, 2000).

Hyperhomocysteinemia unleashes mediators of inflammation and has many other potential damaging effects, for example, it increases production of intracellular superoxide anion causing oxidative stress (Hayden and Tyagi 2004) which is known to be related to the development of diabetes. Since plasma homocysteine levels can be reduced by folic acid and vitamin B6 (Boushey et al. 1995), it seems plausible that intake of these vitamins may provide protection against diabetes.

2.2.4 Dietary pattern hypothesis

The main interest in the link between dietary factors and type 2 diabetes risk has been focused on individual nutrients or food items (Virtanen and Aro 1994; Parillo and Riccardi 2004). However, this approach may be confounded by the effect of dietary patterns (Ursin et al.1993). Instead of isolated nutrients, people eat meals mixing different foods, giving several nutrients a chance to interact. These interactions between nutrients may potentially confound dietary studies on individual foods and nutrients. Multicollinearity between nutrients has also made it extremely difficult to separate the effect of highly correlated individual nutrients in observational dietary studies (Hu 2002). It has been suggested that the effect of the overall diet beyond single foods and nutrients can be studied with dietary pattern analyses (Jacobson and Stanton 1986; Hu 2002). However, empirical evidence on the question of whether the dietary pattern approach can actually assess interaction between nutrients or whether it simply summarizes the effect of individual components is still lacking. Besides the foods and nutrients, it is possible that the dietary patterns also reflect non-dietary factors beyond diet such as regional and cultural factors.

2.3 Review of epidemiological studies linking plant foods and risk of type 2 diabetes

2.3.1 Dietary pattern approach

Three main approaches have been used to define dietary patterns: factor analysis, cluster analysis, and dietary indices (Hu 2002). Factor analysis and cluster analysis are the predominant *a posteriori* methods. Both are used in identifying major dietary patterns independently of their relevance to disease, whereas, the *a priori* approach is used to describe the ideal diet for disease prevention based on available evidence of the disease.

A few studies have recently followed a dietary pattern approach to study the relationship between diet and diabetes prospectively (Table 1). In a study among American male health professionals, a dietary pattern identified by factor analysis was characterized by higher consumption of vegetables, fruit, fish, poultry and whole grains (van Dam et al. 2002a). This “prudent” pattern predicted lower risk of type 2 diabetes during 12 years of follow-up. An almost identical prudent dietary pattern, characterized by fruits, vegetables, whole grain, fish, poultry and low-fat dairy products predicted a modest non-significant inverse association with the risk of type 2 diabetes in women during follow-up of 14 years (Fung et al. 2004). An *a priori*-formed pattern score based on the intake of cereal fiber, polyunsaturated fat, *trans*-fatty acids, and postprandial glycemic load was related to the development of diabetes risk during a 16-year follow-up in the Nurses' Health Study (Hu et al. 2001b). In line with these studies, a vegetarian diet, although not assessed by pattern analysis, has been inversely associated with diabetes mortality. Diabetes mortality was studied on the basis of death certificates in a large cohort of 25 698 White Seventh-day Adventists from California (Snowdon and Phillips 1985). Members of this conservative religious group are encouraged to avoid consumption of meat, fish, eggs coffee, alcohol and tobacco. The study participants completed a questionnaire in which they were asked about potential meat consumption. After 20 years, significantly lower diabetes mortality was observed among vegetarians when compared to non-vegetarians (Table 1).

Cross-sectional analyses of patterns characterized by plant foods have suggested a lower prevalence of impaired glucose tolerance and type 2 diabetes, hyperglycemia and lower fasting insulin content (Table 1). However, in a Canadian study, reduced prevalence of type 2 diabetes was observed only on intermediate values and no linear trend between dietary pattern scores and prevalence of type 2 diabetes was observed (Gittelsohn et al. 1998). However, it should be borne in mind that the results of the cross-sectional studies need to be interpreted with caution as it is impossible to determine whether the higher level of exposure preceded the outcome or vice versa.

Table 1. **A summary of the cohort- and cross-sectional studies that have assessed the association between dietary patterns related to plant foods and the risk of type 2 diabetes or indicators of glucose metabolism**

Reference	Study	Study Population / cases[a]	Follow-up (years)	Diet assessment[b]	Outcome[c]	Exposure	Results[d]	Adjustments[e]
Cohort studies								
Snowdon et al. (1985)	Adventist Health Study	25 698 / 278 F/M	21	Questionnaire on food consumption	DM2 mortality	Vegetarian diet	RR=0.53 (0.32–0.83)[f] Males RR=0.91 (0.63–1.25) Females	Age, sex, body weight, diet[g]
Hu et al. (2001)	The Nurses' Health Study	84 941 / 3300 F	16	FFQ (61 items)	Incidence of DM2	Pattern score based on cereal fiber, PUFA[h], *trans*-fatty acids, and glycemic load	RR=0.49 (0.42–0.56)	Age, BMI, smoking, energy intake, family history of diabetes, time period, menopausal status, hormone therapy
van Dam et al. (2002)	The Health Professionals Follow-up Study	42 504 / 1321 M	12	FFQ (131 items)	Incidence of DM2	Dietary pattern mainly characterized by vegetables and fruits	RR=0.84 (0.70–1.00)	Age, BMI, smoking, energy intake, family history of diabetes, BP, serum cholesterol, alcohol use, time period, ancestry
Fung et al. (2004)	The Nurses' Health Study	69 554 / 2 699 F	14	FFQ (116 itams)	Incidence of DM2	Prudent dietary pattern	RR=0.89 (0.78–1.02)	Age, BMI, smoking, energy intake, PA, family history of diabetes, alcohol use, hypertension, hypercholesterolemia, menopausal status
Cross-sectional studies								
Gittelsohn et al. (1998)	Survey in a Native Canadian community	721 / 116 F / M		FFQ (34 items)	Prevalence of DM2	A pattern characterized by vegetables	OR=0.86 (0.42–1.75)	Age and sex
Fraser et al. (1999)	Adventist Health Study	34 198 / NR		FFQ (51 items)	Prevalence of DM2	Vegetarian diet	OR=0.51(0.40–0.64) Males OR=0.52 (0.45-0.61) Females	Age

Williams et al. (2000)	The Isle of Ely study	802 / 29 F/M	FFQ (35 items)	New DM2	A pattern characterized by vegetables, fruits, fish, pasta and rice	OR=0.54 (0.32–0.91)	Age, sex, BMI, smoking
Fung et al. (2001)	The Health Professionals Follow-up Study	466 / NR M	FFQ (130 items)	Plasma fasting Insulin	Dietary pattern mainly characterized by vegetables and fruits	R=-0.25; P<0.05	Age, BMI, smoking, energy intake, PA, television watching, alcohol use
Wirfält et al. (2001)	Malmö Diet and Cancer study	4 999 / 683 F/M	1-year diet history and a 7-day menu book	Prevalence of HG	Dietary pattern mainly characterized by low-fat and high fiber foods	OR=0.88 (0.56–1.39) Males OR=0.92 (0.67–1.25) Females	Age, body fat, energy intake, past diet change, interviewer, season of data collection

[a]F = females, M = males. [b]FFQ = food frequency questionnaire. [c]DM2 = type 2 diabetes, HG = Hyperglycemia. [d]RR = relative risk between the extreme categories of the exposure, OR = Odds ratio of type 2 diabetes between the extreme categories of exposure, R = Pearson partial correlation coefficient. [e]Adjustments by modeling, BMI = body mass index, BP = blood pressure, PA = physical activity. [f]Further adjusted for physical activity. [g]Consumptions of meat, eggs, milk, fruit, sweet desserts, candy and soft drinks. [h]Polyunsaturated fat.

2.3.2 Individual plant foods

Numerous small-scale clinical trials have suggested benefits in insulin sensitivity by plant food consumption (Kiehm et al. 1976; Simpson et al.1979a; Simpson 1979b; Fukagawa et al. 1990; Venn and Mann 2004). Large-scale interventions on lifestyle modification have supported the hypothesis on the importance of dietary factors in glucose metabolism besides physical activity and weight control (Pan et al.1997; Tuomilehto et al. 2001; Knowler et al. 2002; Mensink et al 2003). Diet and exercise combined in interventions were associated with a reduction of about 60% in the risk of developing type 2 diabetes in high-risk subjects (Tuomilehto et al. 2001; Knowler et al. 2002), as well as significantly decreased fasting insulin levels and 2-hour glucose values (Mensink et al. 2003). Dietary counseling alone was associated with a 31% reduction in diabetes incidence (Pan et al. 1997). In line with these trials, many cohort studies have suggested a reduction of diabetes risk among persons with higher intakes of plant foods, although contradictory results also exist (Table 2).

Lundgren et al.(1989) reported a slightly lower consumption of fruits among women who developed diabetes during a 12-year follow-up, however the difference was not significant in a study population with a low number of subjects (Table 2). A 60% lower risk of type 2 diabetes was observed among persons with a higher intake of legumes at a small cohort of patients of one clinic during follow-up of four years (Feskens et al. 1991).

The analyses of the data from the Nurses' Health Study showed an inverse but non-significant association between vegetable intake, and type 2 diabetes incidence among 84 360 women aged 30 to 55 years with follow-up of six years (Colditz et al. 1992). However, no association was observed for fruit intake. The increase in fruit and vegetable intakes during a 20-year follow-up, but not baseline intake, was inversely associated with 2-h postload glucose values in the Seven Countries Study, in which 338 Dutch and Finnish men were studied (Feskens et al. 1995). In recent analyses based on data from NHANES I, more frequent fruit and vegetable consumption was inversely associated with risk of type 2 diabetes in a sample of 9 665 persons aged 25-74 (Ford and Mokdad 2001). Recently, consumption of nuts and peanut butter was inversely associated with diabetes risk despite a higher energy content of these foods in a large-scale follow-up study among women (Jiang et al. 2002).

In cross-sectional studies, intake of fruits and vegetables, especially green ones have been inversely associated with glycated hemoglobin values (Sargeant et al. 2001) and consumption of tofu and other processed soy products have been inversely associated with prevalence of glycosuria among post-menopausal women but not among pre-menopausal women (Yang et al. 2004). Other cross-sectional studies have mostly suggested an inverse but non-significant association between intake of fruits and vegetables and lower prevalence of newly diagnosed type 2 diabetes and glycosuria (Table 2).

Three cohort studies have suggested a 20 to 30% lower risk of type 2 diabetes among persons in the highest category of whole grain intake than persons in the lowest category and a strong inverse relationship between the consumption of whole grains and fasting insulin levels has been found (Table 3). The results from the Iowa Women's Health Study and the Nurses' Health Study suggested rather consistently a reduced risk of type 2 diabetes at higher level of whole grain consumption in women (Liu et al. 2000; Meyer et al. 2000). These findings were further supported in a cohort of over 40 000 men (Fung et al. 2002). However, cohort studies on diabetes incidence with cohorts pooling men and women are still lacking.

Cross-sectional studies on whole grain that are based on survey data are presented in Table 3. Greater whole grain consumption has been associated with better insulin sensitivity, and lower prevalence of type 2 diabetes and metabolic syndrome (Table 3). Although a causal relationship cannot be found by cross-sectional analyses, it is reasonable to assume that consumption of whole grain or factors related to whole grain consumption could influence glucose metabolism rather than vice versa. However, the existence of chronical disease may have caused some bias in the dietary intake assessment in the cross-sectional studies.

2.3.3 Dietary fiber

Results of previous cohort studies on dietary fiber and incidence of type 2 diabetes have been somewhat inconsistent, but intake of cereal fiber has consistently been shown to have an inverse association with diabetes incidence (Table 4). Fiber derived from vegetables or fruit, however, has not been associated with risk of type 2 diabetes (Salmeron et al. 1997a; Salmeron et al. 1997b; Meyer et al. 2000; Stevens et al. 2002).

Table 2. **A summary of the cohort- and cross-sectional studies that have assessed the association between fruit, vegetables, legumes and nuts and the risk of type 2 diabetes or indicators of glucose metabolism**

Reference	Study	Study population/ cases[a]	Follow-up (years)	Diet assessment[b]	Outcome[c]	Exposure	Results[d]	Adjustments[e]
Cohort studies								
Lundgren et al. (1989)	Gothenburg study	120 / 40 F	12	24-h recall	Intake difference between DM2 cases and non-cases	Fruits Potato	Dif$_1$=-10.9%; NS[f] Dif$_1$=-1.4%; NS	No adjustments
Feskens et al. (1991)	A cohort based on patients of one clinic	175 / 59 M	4	Cross-check dietary history	Insidence of glucose intolerance	Vegetables Fruits Potatoes	Dif$_1$=3.2%; NS Dif$_1$=8.9%; NS Dif$_1$=-3.7; NS	No adjustments
						Legumes	OR=0.40 (0.18–0.90)	Age, BMI, smoking, energy intake, alcohol use
Colditz et al. (1992)	The Nurses' Health Study	84 360 / 702 F	6	FFQ (61 items)	Incidence of DM2	Vegetables Fruits	RR=0.76 (0.50–1.16) RR=1.15 (0.72–1.84)[g]	Age, BMI, energy intake Alcohol use, prior weight change
Feskens et al. (1995)	The Seven Countries Study	338 / 26 M	20	Dietary history	2-h plasma glucose value	Vegetables and legumes Potato Fruit and berries	β=-0.35; NS β=-0.005; NS β=-0.11; NS	Age, BMI, smoking, energy intake, cohort
Meyer et al. (2000)	The Iowa Women's Health Study	35 988 / 1 141 F	6	FFQ (127 items)	Incidence of DM2	Fruit and vegetables Mature beans	RR=1.05 (0.84–1.31) RR=0.96 (0.76–1.20)	Age, BMI, smoking, energy intake, PA, WHR, alcohol use, education,
Ford and Mokdad (2001)	NHANES I	9 665 / 1 018 F/M	20	24 h recall (NR)	Incidence of DM2	Fruit and vegetables	RR=0.79 (0.59–1.06)	Age, sex, BMI, smoking, energy intake, PA, BP, serum cholesterol, alcohol use, education
Jiang et al. (2002)	The Nurses' Health Study	83 818 / 3 206 F	16	FFQ (61 items)	Incidence of DM2	Nuts	RR=0.73 (0.60–0.89)	Age, BMI, smoking, energy intake, PA, Family history of diabetes, alcohol use

Cross-sectional studies

Feskens et al. (1990)	The Zutphen Study	394 / NR M		Cross-check dietary history	Fasting plasma glucose, IAUC	Fruit Legumes	β=-0.09; NS β=-0.05; NS	Age, energy intake, subscapular skinfold thickness
Williams et al. (1999)	The Isle of Ely study	1 122 / 51 F/M		FFQ (35 items)	New DM2	Frequent intake of vegetables Fruits Potato	OR=0.27 (0.06–1.22) OR=0.57 (0.26–1.25) OR=1.92 (0.85–4.33)[h]	Age, sex, BMI, family history of diabetes
Ekblond et al. (2000)	Diet, Cancer and Health	32 807 / 226 F/M		FFQ (192 items)	Prevalence of glycosuria	Vegetables Fruit	OR=0.89(0.79-1.02) Males OR=1.06(0.83-1.36) Females OR=0.97(0.88-1.08) Males OR=0.84(0.67-1.05) Females	Age, BMI, energy intake, PA, WHR
Sargeant et al. (2001)	The EPIC-Norfolk Study	5 996 / NR F/M		FFQ (130 items)	Blood HbA_{1c}	Fruit Green leafy vegetables	Dif_2=1.8%; P=0.007 Dif_2=3.1%; P=0.001	Age, sex, BMI, smoking, energy intake, PA, family history of diabetes, WHR, alcohol use, education, supplement use, vegetarian diet,
Yang et al. (2004)	Shanghai Women's Health Study	39 385 / 323 F		FFQ (NR)	Prevalence of glycosuria	Tofu and processed soy products	OR=1.23(0.53–2.89) Pre-menopausal OR=0.51(0.26–0.98) Post-menopausal	Age, BMI, energy intake, PA, education, TIME, season of recruitment, diet[i]

[a]F = females, M = males, NR = not reported. [b]FFQ = food frequency questionnaire. [c]DM2 = type 2 diabetes, IAUC = incremental area under curve. [d]Dif_1 = difference between cases and non-cases = (cases-non-cases)/non-cases)*100, Dif_2 = difference in blood HbA_{1c} between the lowest and the highest category of the exposure = (Lowest-highest)/lowest)*100, OR = Odds ratio of type 2 diabetes between the extreme categories of exposure, RR = relative risk between the extreme categories of the exposure, β = β coefficient for linear regression for association between dietary exposure and continuous outcome variable. [e]Adjustments by modeling, BMI = body mass index, PA = physical activity, WHR = waist-to-hip-ratio, BP = blood pressure, TIME = time interval between last meal and urine sample collection. [f]NS = Not significant.. [g]Among women with BMI< 29. [h]Further adjusted for socio economic group. [i]Intakes of carbohydrates, fat, non-soy fiber and non-soy protein.

Table 3. A summary of the cohort- and cross-sectional studies that have assessed the association between intake of whole grain and the risk of type 2 diabetes or indicators of glucose metabolism

Reference	Study	Study population/ cases[a]	Follow-up (years)	Diet assessment[b]	Outcome[c]	Results[d]	Adjustments[e]
Cohort studies							
Pereira et al. (1998)	The CARDIA study	3 627 / NR F/M	7	Diet history	Fasting serum insulin	B[f] = -2.44%; P<0.01	Age, sex, BMI, smoking, energy intake, PA, field center, alcohol use, education, race and interaction terms of field center, smoking, education, race and sex
Liu et al. (2000)	The Nurses' Health Study	75 521 / 1879 F	10	FFQ (61 items)	Incidence of DM2	RR=0.73 (0.63–0.85)	Age, BMI, smoking, energy intake, PA , family history of diabetes, alcohol use, supplement use
Meyer et al. (2000)	The Iowa Women's Health Study	35 988 / 1141 F	6	FFQ (127 items)	Incidence of DM2	RR=0.79 (0.65–0.96)	Age, BMI, smoking, energy intake PA, WHR, alcohol use, education,
Fung et al. (2002)	The Health Professionals Follow-up Study	42 898 / 1197 M	12	FFQ (131 items)	Incidence of DM2	RR=0.70 (0.57–0.85)	Age, BMI, smoking, energy intake, PA, Family history of diabetes, alcohol use, fruit and vegetable intakes
Cross-sectional studies							
McKeown et al. (2002)	The Framingham Offspring Study	2941 / NR F/M		FFQ (126 item)	Fasting plasma insulin	Dif=-3%; P=0.03	Age, sex, smoking, energy intake, PA, BP, Alcohol use, FAT, supplement use
Liese et al. (2003)	The Insulin Resistance and Atherosclerosis Study	1600 / NR F/M		FFQ (114 items)	Insulin sensitivity	β=0.04; P = 0.03	Age, sex, BMI, smoking, energy intake, family history of diabetes, WC, ethnicity, clinic, energy expenditure
Esmaillzadeh et al. (2004)	Teheran Lipid and Glucose Study	827 / NR F/M		FFQ (NR)	New DM2	OR=0.88 (0.80–0.94)	Age, sex, smoking, energy intake, BP, energy from fat, estrogen use, diet[g]
McKeown et al. (2004)	The Framingham Offspring Study	2 834 / F/M		FFQ (126 item)	Prevalence of metabolic syndrome	OR=0.67 (0.48-0.91)	Age, sex, smoking, energy intake, PA, alcohol use, FAT, multivitamin use, BP

[a]F = females, M = males, NR = not reported. [b]FFQ = food frequency questionnaire. [c]DM2 = type 2 diabetes. [d]RR = relative risk between the extreme categories of the exposure, β = β coefficient for linear regression for association between dietary exposure and continuous outcome variable, Dif = Difference in fasting insulin between the extreme quintiles of whole grain intake (highest-lowest/highest*100), OR = Odds ratio of type 2 diabetes between the extreme categories of exposure. [e]Adjustments by modeling, BMI = body mass index, PA = physical activity, WHR = waist-to-hips ratio, WC = waist circumference, BP = blood pressure, FAT = intakes of saturated fat and polyunsaturated fat. [f]Repeated measures regression, expected change in fasting insulin (%) per change in intake frequency of the intake. [g]Consumption of meat, fish, fruit and vegetables.

Colditz et al. (1992) reported an inverse, but non-significant association between total fiber intake and diabetes risk among women with a body mass index less than 29 kg/m^2 in analyses based on the Nurses' Health Study. Salmeron et al. (1997a) also analyzed the data based on the Nurses' Health Study, but used dietary data collected at a later date with a more specific food frequency questionnaire. In line with the earlier analysis by Colditz et al. (1992), a significant inverse association between dietary fiber and incidence of type 2 diabetes was observed. These findings were further supported by the results from the Iowa Women's Health Study (Meyer et al. 2000), but analyses among men (Feskens et al. 1991; Feskens et al.1995; Salmeron et al. 1997b) and younger women (Schulze et al. 2004) and a cohort of men and women (Stevens et al. 2002) have failed to demonstrate any association between dietary fiber and incidence of type 2 diabetes or glucose intolerance.

Of the fiber derived from plant food sources, cereal fiber has consistently shown a significant inverse association with type 2 diabetes risk (Table 4), although no association was observed among women with a body mass index lower than 29 (Colditz et al. 1992). In the analysis based on the Nurses' Health Study, an approximately 30% lower risk of type 2 diabetes was observed among persons in the highest quintile of cereal fiber intake compared with persons in the lowest quintile (Salmeron et al.1997a). The finding was independent of the main risk factors of diabetes. The finding was further supported in the Iowa Women's Health Study (Meyer et al. 2000) and in later analysis based on the same cohort with extended follow-up of 16 years (Hu et al. 2001b). Cereal fiber intake was also strongly associated with a reduced diabetes risk in the analysis of data from the Nurses' Health Study II that consisted of 91 249 women aged 24–44 years (Schulze et al. 2004). As in women, a 30% lower risk was also observed among 42 000 men with higher cereal fiber intake in the Health Professionals Follow-up Study (Salmeron et al.1997b). Stevens et al. (2002) found ethnic differences in the association between cereal fiber intake and diabetes development. A cohort of 12 251 Afro-American and white men and women were followed-up for nine years. A slight but significant inverse association was observed between cereal fiber intake and diabetes risk among whites, but there was no association among Afro-Americans.

In cross-sectional analyses of survey data, dietary fiber intake has been inversely associated with fasting insulin values, insulin resistance and prevalence of type 2 diabetes, glycosuria and metabolic syndrome (Table 5). Some studies have failed to observe any associations at all (Marshall et al. 1991; Hodge et al. 1996) and one study suggested a difference in the association by gender (Vitelli et al. 1996). In a smaller scale cross-sectional analysis (not included in Tables) dietary fiber intake was correlated with better insulin sensitivity (Lovejoy and DiGirolamo 1992).

Table 4. **A summary of the cohort studies that have assessed the association between consumption of dietary fiber and cereal fiber and the risk of type 2 diabetes or indicators of glucose metabolism**

Reference	Study	Study population/ cases[a]	Follow-up (years)	Diet assessment[b]	Outcome[c]	Exposure	Results[d]	Adjustments[e]
Feskens et al. (1991)	A cohort based on patients of one clinic	175 / 59 M	4	Cross-check dietary history	Incidence of glucose intolerance	Total fiber	Dif=0.9%; NS[f]	No adjustments
Colditz et al. (1992)	The Nurses' Health Study	84 360 / 702 F	6	FFQ (61 items)	Incidence of DM2	Total fiber Cereal fiber	BMI ≥ 29: RR=1.08(0.78–1.48) BMI <29: RR=0.75(0.50–1.13) BMI<29: RR=0.98(0.62–1.55)[g]	Age, BMI, smoking, energy intake, family history of diabetes, alcohol use, prior weight change, time period
Hodge et al. (1993)	Population based survey of adults on Pacific island of Nauru	177 / 7 F/M	5	24-h diet recall	Incidence of DM2	Total fiber	OR=0.69 (0.16-2.96)	Age, sex, BMI
Feskens et al. (1995)	The Seven Countries Study	338 / 26 M	20	Cross–check diet history	2-h plasma glucose value	Total fiber	β=-0.11; NS	Age, BMI, smoking, energy intake cohort
Salmeron et al. (1997a)	The Nurses' Health Study	65 173 / 915 F	6	FFQ (134 items)	Incidence of DM2	Total fiber Cereal fiber	RR=0.78(0.62–0.98) RR=0.72(0.58–0.90)	Age, BMI, smoking, PA, family history of diabetes, alcohol use,
Salmeron et al. (1997b)	The Health Professionals Follow-up Study	42 759 / 523 M	6	FFQ (131 items)	Incidence of DM2	Total fiber Cereal fiber	RR=0.98(0.73–1.33) RR=0.70(0.51–0.96)	Age, BMI, smoking, PA, family history of diabetes, alcohol use,
Meyer et al. (2000)	The Iowa Women's Health Study	35 988 / 1 141 F	6	FFQ (127 items)	Incidence of DM2	Total fiber Cereal fiber	RR=0.78(0.64–0.96) RR=0.64(0.53–0.79)	Age, BMI, smoking, energy intake, PA, WHR, alcohol use, education
Hu et al. (2001b)	The Nurses' Health Study	84 941 / 3 300 F	16	FFQ (61 items)	Incidence of DM2	Cereal fiber	Higher intake predicted significantly lower risk. Point estimate not reported.	Age, BMI, smoking, energy intake, family history of diabetes, PA, menopausal status, hormone therapy, alcohol use, PUFA/ SAFA ratio, trans-fat, glycemic load

Stevens et al. (2002)	The Atherosclerosis Risk in Communities (ARIC)study	12 251 / 1 447 F/M	9	FFQ (66 items)	Incidence of DM2	Total fiber	RR=1.00(0.99–1.01)[h] Whites, RR=1.00(0.98–1.02)[h] African Americans	Age, sex, BMI, smoking, PA, field center, education
						Cereal fiber	RR=0.75(0.60–0.92) Whites, RR=0.86(0.65–1.15) African Americans	
Schulze et al. (2004)	The Nurses' Health Study II	91 249 / 741 F	8	FFQ (133 items)	Incidence of DM2	Total fiber Cereal fiber	RR=1.00(0.75–1.34) RR=0.63(0.47–0.85)	Age, BMI, smoking, BP, family history of diabetes, alcohol use, postmenopausal hormone use, oral contraceptive use, glycemic load, magnesium and caffeine intakes

[a]F = females, M = males. [b]FFQ = food frequency questionnaire. [c]DM2 = type 2 diabetes. [d]Dif = difference between cases and non-cases = (cases-non-cases) / non-cases)*100, RR = relative risk of type 2 diabetes between the extreme categories of exposure, OR = Odds ratio of type 2 diabetes between the extreme categories of exposure, β = β coefficient for linear regression for association between dietary exposure and continuous outcome variable. [e]Adjustments by modeling, BMI = body mass index, PA = physical activity, WHR = waist -to-hip ratio, BP = blood pressure. [f]Not significant. [g]Not adjusted for energy intake and smoking. [h]Relative risk for increment of 1g/day.

Table 5. **A summary of the case-control and cross-sectional studies based on survey data reporting the relationship between dietary fiber intake and type 2 diabetes or indicators of glucose metabolism**

Reference	Study	Study population/ cases[a]	Diet assessment[b]	Outcome[c]	Results[d]	Adjustments[e]
Manolio et al. (1991)	The CARDIA study	5115 / NR F/M	28-day diet history interview	Fasting serum insulin	R_1=-0.10, P< 0.01	No adjustments
Marshall et al. (1991)	The San Luis Valley Diabetes Study	1 146 / 70 F/M	24-h recall	Difference between incident cases of DM2 and non-cases	Dif=-12.9 NS[f]	Age, sex, energy intake, ethnicity
Feskens et al. (1994)	The Zutphen Elderly Study	389 / NR M	Cross-check dietary history	Insulin level during oral glucose tolerance test	R_2=-0.12, P<0.05	Age, BMI, smoking, energy intake, PA, ratio of subscapular to triceps skinfold thickness, CHD, prescribed diets
Hodge et al. (1996)	Survey of Wanigela people on Pacific island of Nauru	145 CA[g] 140 CO	FFQ (87 items)	New DM2	OR=1.06 (0.99–1.13)	Age and sex (matched) Age, sex, BMI, PA, WHR (in the model)
Vitelli et al. (1996)	The Atherosclerosis Risk in Communities (ARIC) Study	13 167/ NR F/M	FFQ (61 item)	Fasting serum insulin	IQR=0.6% (-1.1–2.3) Males IQR=-2.9% (-4.4– -1.5) Females	Age, BMI, smoking, energy intake, PA, WHR, race
Wolever et al. (1997)	A Survey in Sandy Lake community	272 / 23 F/M	24-h recall	New DM2	OR=0.61 (0.39–0.94)[h]	Age, sex, BMI
Ekblond et al. (2000)	Diet, Cancer and Health	32 807 / 226 F/M	FFQ (192 items)	Prevalence of glycosuria	OR=0.68(0.51–0.91) Males OR=0.71(0.37–1.37) Females	Age, BMI, energy intake, PA, WHR
Ylönen et al. (2003a)	The Botnia Dietary Study	552 / NR F/M	3-day food records	Insulin resistance	β=-0.17; P = 0.012	Age, sex, BMI, smoking, energy intake, WHR, BP, education, serum triglyserides, HDL cholesterol
McKeown et al. (2004)	The Framingham Offspring Study	2 834 / F/M	FFQ (126 item)	Prevalence of metabolic syndrome	OR=0.73(0.51–1.03)	Age, sex, smoking, energy intake, PA, alcohol use, BP, FAT, multivitamin use

[a]F = females, M = males, NR = not reported. [b] FFQ = food frequency questionnaire. [c]DM2 = type 2 diabetes. [d]Dif = Difference between cases and non-cases = (cases-non-cases)/non-cases)*100, R_1 = Pearson correlation coefficient, R_2 = Spearman rank correlation coefficient, OR = Odds ratio of type 2 diabetes between the extreme categories of exposure, IQR = predicted difference in fasting insulin for inter quartile range; β = β coefficient for linear regression for association between dietary exposure and continuous outcome variable. [e]Adjustments by modeling, BMI = body mass index, PA = physical activity, CHD = prevalence of coronary heart disease, WHR = waist-to-hip ratio, BP = blood pressure, FAT = intakes of saturated fat and polyunsaturated fat. [f]Not significant. [g]Case-control design, CA = cases, CO = controls. [h]Risk of diabetes associated with a 1-SD increase in intake based on distribution in persons free from diabetes.

2.3.4 Antioxidant components

A total of four follow-up studies have assessed the association between intakes or serum levels of antioxidant vitamins and incidence of type 2 diabetes or 2-hour glucose tolerance test values (Table 6). The results have been somewhat controversial. A large long-term intervention among healthy male physicians failed to demonstrate a significant change in the risk of type 2 diabetes with β-carotene supplementation (Liu et al. 1999). A supplementation of 50 mg β-carotene on alternate days was studied in this double-blind placebo-controlled trial of 22 071 healthy men. Incidence of type 2 diabetes did not differ between the treatment group and the placebo group after supplementation over 12 years.

Salonen et al. (1995) reported an inverse association between serum α-tocopherol and diabetes risk in a cohort of 944 middle-aged men from eastern Finland. In a nested case-control study based on the data from Mobile Clinic Health Examination Survey, serum α-tocopherol concentration was not significantly associated with a reduced risk of type 2 diabetes after adjustment for potential confounders (Reunanen et al. 1998). However, a nested case-control study from the same study population showed a strong inverse association between serum α-tocopherol and risk of type 1 diabetes (Knekt et al. 1999). A strong inverse association between vitamin E intake and risk of type 2 diabetes was found among persons who did not use vitamin supplements, but not among supplement users in a follow-up study based on data from the Insulin Resistance and Atherosclerosis Study (Mayer-Davis et al. 2002).

In the Finnish and the Dutch cohorts of the Seven Countries Study, a higher intake of vitamin C at baseline in 1969–1970 predicted significantly lower 2-hour glucose tolerance test values among 338 men performed after 20 years (Feskens et al.1995). Reunanen et al. (1998) reported no association between serum β-carotene and incidence of type 2 diabetes in a nested case-control study based on the data from the Mobile Clinic Health Examination Survey.

A summary of the cross-sectional studies on antioxidant vitamins based on the survey data is presented in Table 6. In these cross-sectional studies, intake of vitamin E has been inversely associated with a high level of glycated hemoglobin (Boeing et al. 2000) and plasma tocopherol content with fasting insulin level (Öhrvall et al. 1993), although some studies have contradictory results (Shoff et al. 1993; Sanchez-Lugo et al. 1997). Ylönen et al. (2003b) reported significant inverse association between dietary α-tocopherol and fasting plasma glucose concentration in women but not in men, and no association between plasma levels of α-tocopherol and fasting glucose.

In small-scale cross-sectional analyses (not shown in Tables) statistically significant inverse correlations were found between insulin-mediated glucose disposal and serum α-carotene, β-carotene and lutein (Facchini et al. 2000), but there was no independent relation between insulin-mediated glucose disposal and intakes of vitamins C and E (Facchini et al. 1996). In small-scale case-control studies that were not based on survey data, blood α-tocopherol concentrations among persons with diabetes have appeared to be lower (Polidori et al. 2000), equal (Leinonen et al. 1998; Abahusain et al. 1999), or even higher than among controls (Vatassery et al.1983).

Some cross-sectional studies have investigated vitamin C and type 2 diabetes or indicators of glucose metabolism (Table 6). Vitamin C intake has been inversely associated with plasma glycated hemoglobin (Shoff et al. 1993; Boeing et al. 2000) and plasma vitamin C concentration with prevalence of hyperglycemia (Sargeant et al. 2000). However, contradictory results exist, (Sanchez-Lugo et al. 1997; Wolever et al. 1997; Will et al. 1999). Numerous small-scale case-control and cross-sectional studies have compared vitamin C status between persons with type 1 or 2 diabetes and those free of the disease (Will and Byers 1996).

Population-based cross-sectional studies on carotenoids and diabetes give inconsistent results (Table 6). In a Finnish cross-sectional study on persons with high risk of type 2 diabetes, intakes of α- and β-carotene, lycopene and plasma β-carotene concentrations were inversely associated with fasting plasma glucose concentration (Ylönen et al. 2003b). In small-scale case-control and cross-sectional studies (not shown in Tables), serum carotenoid levels have been reported to be lower in persons with diabetes than in persons free of diabetes in several (Rock et al. 1997; Abahusain et al. 1999; Polidori 2000; Facchini et al. 2000), but not in all studies (Ramachandran 1973). Of the other dietary components with antioxidant properties, flavonoid intake has recently been found to be related to a reduced incidence of type 2 diabetes (Knekt et al. 2002).

Table 6. A summary of the studies that have assessed the association between dietary intakes or blood concentrations of antioxidant vitamins and development of type 2 diabetes or indicators of glucose metabolism

Reference	Study	Study population/ cases[a]	Follow-up (years)	Assessment tool[b]	Outcome[c]	Exposure	Results[d]	Adjustments[e]
Cohort studies								
Feskens et al. (1995)	The Seven Countries Study	338 / 26 M	20	Cross-check dietary history	2-h plasma glucose value	Vitamin C	β=-0.03, P < 0.05	Age, BMI, smoking energy intake, cohort
Salonen et al. (1995)	The Kuopio Ischaemic Heart Disease Risk Factor Study	944 / 45 M	4	Lipid standardized serum level	Incidence of DM2	α-tocopherol	RR=0.26 (0.12–0.57)	Age, BMI, smoking, socioeconomic status, ratio of serum saturated fat to sum of unsaturated
Reunanen et al. (1998)	The Mobile Clinic Health Examination Survey	106 CA[f] 201 CO F/M	20	Serum level	Incidence of DM2	α-tocopherol β-carotene	RR=0.78 (0.28–2.20) RR=1.53 (0.51–4.64)	Age, sex, BMI, smoking energy intake, hypertension, serum cholesterol, plasma glucose
Mayer-Davis et al. (2002)	The Insulin Resistance and Atherosclerosis Study	895 / NR F/M	5	FFQ (114 items)	Incidence of DM2	α-tocopherol	RR=1.37 (0.11–17.18) Supplement users RR=0.12 (0.02–0.68) Non–supplement users	Age, sex, BMI, smoking energy intake, PA, family history of diabetes, WC, GLUC, ethnicity, clinic, general health, diet[g]
Cross-sectional dietary studies								
Shoff et al. (1993)	Beaver Dam Eye Study	2 147 / NR		1-y diet-history	Plasma HbA_{1c}	Vitamin E Vitamin C β-carotene	β=-0.023; NS[h] β=-0.041; P<0.05 β=-0.021; NS	Age and sex
Sanchez-Lugo et al. (1997)	The Insulin Resistance and Atherosclerosis Study	1 151/ NR F/M		FFQ (114 item)	Rank of insulin sensitvity	Vitamin E Vitamin C	β= 0.02; P = 0.63 β=-0.005; P = 0.75	Age, sex, BMI, smoking, energy intake, PA, WHR, alcohol use, education, income, blood cholesterol, CVD- conditions[i]
Wolever et al. (1997)	A Survey in Sandy Lake community	630 / 23 F/M		24-h recall	New diagnosed diabetes	Vitamin C	OR=1.00 (0.69–1.44)	Age, sex, BMI
Boeing et al. (2000)	The EPIC-Potsdam Study	1 773 / NR F/M		FFQ (146 item)	Prevalence of high HbA_{1c}	Vitamin E Vitamin C β-carotene	OR=0.65 (0.43–0.96) OR=0.50 (0.33–0.74) OR=0.77 (0.52–1.13)[j]	Age, sex, BMI, smoking energy intake, PA, education, supplement use

Ylönen et al. (2003b)	The Botnia Dietary Study	182 / NR F/M	3-d food record	Fasting plasma glucose	α-tocopherol β-carotene	β=-0.07;P=0.81 Males β=-0.54;P=0.03 Females β=-0.24;P=0.006 Males β=0.02;P=0.74 Females	Age, sex, BMI, smoking energy intake, WHR, education
Cross-sectional blood studies							
Öhrvall et al. (1993)	A Health survey of risk factors for coronary heart disease	906 / NR F/M	Plasma level	Fasting serum insulin	Lipid corrected α-tocopherol	R=-0.11; P = 0.0008	No adjustments
Ford et al. (1999)	NHANES III	1 435 / 148 F/M	Serum level	2-h blood glucose value	β-carotene β-cryptoxanthin	β=-0.001; P = 0.007 β=-0.001; P = 0.05	Age, sex, BMI, smoking energy intake, race, education, serum cotinine, serum cholesterol, PA, alcohol use, vitamin use, carotene intake
Will et al. (1999)	NHANES III	2 040 / 237 F/M	Serum level	Difference between DM2 cases and non-cases	Vitamin C	Dif=-11.6%; NS	Age, sex, BMI, smoking energy intake, race, PA, alcohol use, education, duration of fast.
Sargeant et al. (2000)	The EPIC-Norfolk Study	6 458 / 44 F/M	Plasma level	Prevalent new HG	Vitamin C	OR=0.70 (0.52–0.95)	Age, sex, BMI, smoking energy intake, WHR, education, supplement use, vegetarian diet, alcohol use, PA, diet[k]
Ylönen et al. (2003b)	Botnia Dietary Study	182 / NR F/M	Plasma level	Fasting plasma glucose	α-tocopherol β-carotene	β=0.09;P=0.83 Males β=0.09;P=0.85 Females β=-0.21;P=0.15 Males β=0.25;P=0.03 Females	Age, sex, BMI, smoking energy intake, WHR, education

[a]F = females, M = males. [b]FFQ = food frequency questionnaire. [c]DM2 = type 2 diabetes, HG = hyperglycemia. [d]RR = relative risk of type 2 diabetes between the extreme categories of exposure, β = β coefficient for linear regression for association between dietary exposure and continuous outcome variable, OR = Odds ratio of type 2 diabetes between the extreme categories of exposure, R = Pearson partial correlation coefficient, Dif = Difference between cases and non-cases = (cases-non-cases)/non-cases)*100. [e]Adjustments by modeling, BMI = body mass index, PA = physical activity, GLUC = baseline glucose tolerance, WC = Waist circumference. [f]Nested case-control design, CA = cases, CO = controls, [g]Intakes of fat, fiber, alcohol and magnesium. [h]NS = not significant. [i]CVD-conditions consists self-reported angina, hypertension, myo-cardial infarction and stroke. [j]Not adjusted for supplement use. [k]Diet = vegetarian diet, dietary vitamin E, dietary fiber, dietary saturated fat.

2.3.5 Other components of plant foods

Large American prospective studies have demonstrated an inverse association between dietary magnesium and the risk of type 2 diabetes (Colditz et al.1992; Salmeron et al.1997a; Salmeron et al.1997b; Lopez-Ridaura et al.2004). However, two other studies failed to demonstrate this inverse association (Kao et al.1999; Meyer et al.2000). In human experimental studies, some (Paolisso et al.1989; Paolisso et al.1992; Paolisso et al.1994b), but not all (de Valk et al. 1998) have shown the beneficial result of magnesium supplementation on glucose metabolism or insulin sensitivity. Decreased erythrocyte and plasma potassium concentrations have been associated with glucose intolerance (Modan et al. 1987). Intervention studies of chromium on glucose and insulin responses have shown no effect among persons free of diabetes (Uusitupa et al. 1992; Althuis et al. 2002).

Vegetable fat has been associated with a reduced diabetes risk in several previous follow-up studies (Colditz et al. 1992; Salmeron et al. 2001; Meyer et al. 2001; Laaksonen et al. 2002). However, contradictory findings exist (Marshall et al. 1994; Mooy et al. 1995; Feskens et al. 1995; Salmeron et al. 1997a; van Dam et al. 2002b). Available data on the specific type of fatty acids consumed and development of type 2 diabetes suggest a potential beneficial effect of polyunsaturated fatty acids (Trevisan 1990; Feskens et al. 1994; Mayer-Davis et al. 1997; Salmeron et al. 2001) and a potential adverse effect of saturated fatty acids (Maron et al. 1991; Parker et al. 1993; Mayer et al. 1993; Feskens et al. 1994; Vessby et al. 1994; Marshall et al. 1997; Vessby et al. 2001; Wang et al. 2003). With the exception of one study on patients with impaired glucose tolerance (Marshall et al. 1994), epidemiological studies have failed to find an association between monounsaturated fatty acids and risk of type 2 diabetes (Colditz et al. 1992; Feskens et al. 1995; Salmeron et al. 1997b). Monounsaturated fatty acids have also been positively associated with insulin concentrations (Maron et al. 1991; Mayer et al. 1993), but the association could be due to correlation with saturated fatty acids (Hu et al. 2001c).

Epidemiological evidence on phytoestrogens and glucose metabolism is almost non-existant. In one cross-sectional study, dietary isoflavone consumption has been inversely associated with fasting and 2-h postload insulin levels among postmenopausal women (Goodman-Gruen & Kritz-Silverstein, 2001). A human intervention study demonstrated a beneficial effect of a soy phytoestrogen supplementation on glucose metabolism among persons with diabetes (Jayagopal et al. 2002), although no change in glycated hemoglobin level was observed in another study (Hermansen et al. 2001).

Elevated plasma homocystein level has been related to diabetes complications (Colwell et al. 1997) and prospective studies have suggested a stronger relationship between homocystein and mortality in persons with diabetes than without diabetes (Audelin and Genest 2001). Higher plasma concentrations of homocystein have been found in persons with diabetes in some studies (Chico et al. 1998; Cronin et al. 1998; Hofmann et al. 1998). However, several studies have reported normal homocysteine concentrations in persons with diabetes (Audelin and Genest 2001). To date, there are no prospective studies that have examined the relationship between elevated levels of homocysteine and the incidence of type 2 diabetes.

Epidemiologic evidence suggests that replacing high glycemic index forms of carbohydrate with low ones will reduce the risk of chronic diseases (Jenkins et al. 2002). Among persons with diabetes, the consumption of foods with a low glycemic index has been shown to improve glycemic control (Willett et al. 2002; Opperman et al. 2004). Large-scale cohort studies have shown direct association between the glycemic index and glycemic load with diabetes incidence (Salmeron et al. 1997a; Salmeron et al.1997b; Schulze et al. 2004). However, no association was found either for the glycemic index or glycemic load in the Iowa Women Study (Meyer et al. 2000).

2.3.6 Summary of the epidemiological studies

Besides a vegetarian diet, a prudent dietary pattern characterized by plant food consumption has been associated with reduced risk of type 2 diabetes and specific components of plant foods suggested a strong inverse association with the risk of type 2 diabetes (Table 1). Studies on fruits, vegetables, legumes and nuts have given rather inconsistent results. The inconsistent results are probably due to differences in methods used in these studies, especially the adjustments used. The role of whole grains in the prevention of type 2 diabetes has been demonstrated consistently in four cohorts (Table 3). In the recent meta-analysis that included prospective studies of whole grain and fiber intakes and risk of type 2 diabetes, the pooled relative risk estimate for type 2 diabetes risk was 0.70 (CI = 0.64–0.76) (Liu 2003a).

Epidemiological evidence on the dietary fiber intake and development of type 2 diabetes is rather inconclusive (Tables 4 and 5). However, large cohort studies on cereal fiber intake have rather consistently suggested a reduced risk of type 2 diabetes. Epidemiological evidence on antioxidant vitamins is based mainly on cross-sectional studies with relatively contradictory results (Table 6).

To sum up, studies on dietary patterns are few. Results of the cohort studies on plant foods as well as dietary fiber and antioxidant vitamins in the prevention of diabetes are inconsistent. The role of plant foods, dietary fiber and antioxidant vitamins in the prevention of type 2 diabetes remains to be established. More comprehensive large-scale follow-up studies are needed before firm conclusions can be drawn.

3 AIMS OF THE STUDY

The aim of this study was to investigate the association between consumption of plant foods and incidence of type 2 diabetes using a so called top-down strategy on three levels. First, a pattern mainly characterized by plant foods was studied as a top-level association. Second, food items by plant food origin were studied as intermediate-level associations and finally, fiber and antioxidant vitamins were studied for bottom-level associations. More specific objectives of the study were:

1. to identify major dietary patterns in representative data on Finns (Study I)
2. to study whether the incidence of type 2 diabetes can be predicted by a dietary pattern characterized by plant foods (top-level associations, Study I)
3. to study whether consumption of individual plant foods predicts the incidence of type 2 diabetes (intermediate-level associations, Studies II and III)
4. to test the fiber and antioxidant hypotheses, that relate plant foods to prevention of type 2 diabetes (bottom-level associations, Studies III and IV)
5. to explore to what extent the individual foods of the identified dietary patterns accounted for the associations observed (Study II).

4 POPULATION AND METHODS

4.1 Population

The subjects of the study were drawn from the Finnish Mobile Clinic Health Examination Survey carried out by the Social Insurance Institution during the period 1966–1972 (Aromaa 1981). The baseline examinations were carried out in 34 rural, industrial or semi-urban populations in six regions of the country. A total of 57 440 persons aged 15 or over participated in the baseline study. The average participation rate was 82% for men and 83% for women. A dietary history interview of 10 054 persons was included in the study since 1967 (Järvinen 1996). The dietary patterns were identified among these 10 054 persons. The study population comprised 4344 men and women, after including only individuals aged 40–69 and excluding previously known or newly diagnosed persons with diabetes at baseline. After further exclusion of those who reported a daily energy intake of less than 800 or more than 6000 kcal, the study population comprised 4316 persons (Study III) and after further exclusion of pregnant women, the study population comprised 4304 persons (Studies I, II, IV).

Data from the re-examination survey was used to estimate the reliability of the dietary variables. The health examination survey was repeated after four to seven years in 12 populations of the baseline study in 1973–1976. Altogether, 8 776 men and 8 775 women (90.1% of the sample) who had participated in the baseline examination were re-examined. Dietary data were collected for 4 343 randomly selected persons (Järvinen et al.1993a). Of these, 1844 persons had also had the dietary interview at the baseline assessment.

4.2 Methods

4.2.1 Assessment of non-dietary factors

All participants completed a self-administered questionnaire that was checked at the baseline examination. The questionnaire yielded information on occupation, current pregnancy, babies born with birth weight over 4 500 g, previous and current illnesses, consumption of medicines, family history of diabetes in first-degree relatives, and health-related habits, such as smoking. Occupations were grouped into 9 categories according to the Nordic Standard Classification of occupations (Brockington 1967). The subjects were classified according to smoking status as never-smokers, ex-smokers, smokers of pipes or cigars only, smokers of less than 15 cigarettes per day, and smokers of 15 or more cigarettes per day (Knekt 1988).

In the baseline examinations, body weight and height were measured in light clothing without shoes and the body mass index (kg/m^2) was calculated (Heliövaara and Aromaa 1980). Casual blood pressure was measured with the auscultatory method (Aromaa 1981). Four hypertension categories were formed on the basis of systolic (SBP) and diastolic blood pressure (DBP) and antihypertensive medication (Knekt 1988). Persons with SBP ≥ 170 mmHg and DPB ≥ 100 mmHg and persons using antihypertensive medication were considered to be definitely hypertensive. Persons with SBP ≥ 160 mmHg and DBP ≥ 95 mmHg but not defined as hypertensive were considered to have mild hypertension, and those with SBP < 140 mmHg and DBP < 90 mmHg were considered normotensive. All persons with intermediate values were considered to have borderline hypertension.

Venous blood samples were collected at one hour after an oral glucose dose and participants were asked to fast at least four hours before the examination (Aromaa 1981). An oral glucose tolerance test was included in the examination. The test was carried out for every examinee except known persons known to have diabetes. The oral glucose loads as a 20% solution with three fixed doses of glucose (60, 75 or 90 g) were used according to body size. For practical reasons, the venous blood sample was drawn only once, 1 hour after the oral glucose load (Reunanen et al. 1983). The concentration of glucose in the plasma sample was determined by an autoanalyzer modification of the ferricyanide reduction method (Hoffman 1937). Serum cholesterol concentration was determined from frozen samples with an autoanalyzer modification of the Liebermann-Burchard reaction (Huang et al. 1961).

Known cases of diabetes were identified by information given by the participants at baseline. Persons who were found to have a grossly abnormal (14.0 mmol/l) value in the 1-h glucose tolerance test were invited to a re-examination a few weeks or months later to confirm the diagnosis. Fasting capillary blood glucose values of 7.8 mmol/l or more at the re-examination allowed definite diabetes diagnosis according to the diagnostic criteria of the World Health Organization (WHO 1985). Possible diabetes was considered as fasting capillary blood glucose values of 6.7 – 7.7 mmol/l at the re-examination or a 2-h glucose value of 11.2 mmol or over. All the individuals known to have diabetes and persons with new definite or possible diabetes at baseline were excluded from the analyses in the present study.

4.2.2 Assessment of diet

Total habitual food consumption during the previous year was estimated, using a dietary history interview (Järvinen 1996). The interviews were conducted by home economics technicians, nutritionists or students of nutrition who were specifically trained for this study. Interviewers used a questionnaire form listing over 100 food items and mixed dishes common in the Finnish diet at the time of the dietary study. Several questions were open-ended and left the respondent an opportunity to specify answers and give further details during the interview. Food models were used as an aid in recalling portion sizes. Consumption of foods was estimated per day, week, month, or year according to the choice of the respondent. The method of food preparation was specified. Individual consumption of food items and mixed dishes was converted to grams per day. Thereafter, the ingredients of mixed dishes were broken down into their components using a recipe file and the consumption of food items was calculated per day.

4.2.3 Food composition values

Energy intake was calculated based on the intake of protein, fat and available carbohydrate. Vitamin C, pyridoxine and folic acid contents in food items were derived from Finnish food composition tables (Rastas et al. 1989). Food composition data on fiber (Varo et al. 1984a; Varo et al. 1984b), fatty acids (Hyvönen et al. 1993; Hyvönen and Koivistoinen 1994), vitamin E components (Piironen 1986), and carotenoids (Heinonen 1990) were completed, utilizing analyzed values of Finnish foods. The vitamin E activity of α-tocopherol equivalents was estimated from tocopherols and tocotrienols using published factors (McLaughlin and Weihrauch 1979). The intake of flavonoids was estimated using Dutch food composition values (Hertog et al. 1993; Hertog 1994). For the berries that were missing in the Dutch analyses and which were commonly used in Finland, the flavonoid intake was completed using recently analyzed values for Finnish berries (Häkkinen et al. 1999).

4.2.4 Repeatability of the dietary methods

The repeatability of the dietary history method was estimated after 4–8 months in a subpopulation of 93 individuals and in a subpopulation of 1 844 individuals by repeating the interview after 4–7 years (Järvinen et al.1993a). The reliability coefficients for short-term repeatability were 0.63 for vegetables, 0.55 for fruits and berries, 0.62 for total grain intake and 0.65 for total fiber intake. The short-term reliability coefficient for vitamin E was 0.78 and for vitamin C and β-carotene 0.53

and 0.56, respectively (Järvinen et al. 1993a). The corresponding coefficients for individual tocopherols and tocotrienols varied from 0.58 (γ-tocotrienol) to 0.82 (γ-tocopherol) and the range of reliability coefficients for the other carotenoids considered varied from 0.25 (γ-carotene) to 0.57 (α-carotene).

The long-term reliability coefficients for 4–7 years were 0.47 for vegetables, and 0.39 for fruit and berries. For total grain intake the corresponding long-term reliability coefficient was 0.39. The coefficient of long-term repeatability for total fiber intake was 0.39. The long-term repeatability for vitamin E was 0.34 and for vitamin C the corresponding value was 0.42 and for β-carotene 0.43 (Järvinen et al. 1993a). For individual tocopherols and tocotrienols the long-term reliability coefficient varied from 0.17 (γ-tocotrienol) to 0.53 (β-tocotrienol). For carotenoids other than β-carotene the intraclass correlation coefficients measuring long-term agreement varied from 0.24 (γ-carotene) to 0.43 (β-carotene).

4.2.5 Recognition of diabetes cases

During a 23-year follow-up until the end of 1995, a total of 383 (164 male and 219 female) incident cases were identified from a nationwide registry of patients receiving drug reimbursement, maintained by the Social Insurance Institution (Reunanen et al. 1998). During the first 10-years of follow-up, the number of incident cases was 156 out of 4 316 persons (Study III). Participants in the present study were linked to this register by individual social security codes assigned to each Finnish citizen. The individual follow-up refers to the period of observation from the time of the baseline examination until onset of the disease, death or the end of the observation period, whichever came first.

4.2.6 Statistical methods

Factor analysis (Kim and Mueller 1978) was used to identify dietary patterns among 10 054 persons with collected dietary data (Study I). First of all, the food items had to be grouped before running factor analysis to identify dietary patterns. The food items were grouped into 24 food groups based on the nutrient profile and culinary use of the item. The grouping is presented in Appendix table 1. The principal component method with Varimax rotation was applied in the factor analysis and SAS software was used for the analyses to identify the dietary patterns (SAS/STAT 1989; Hu et al. 1999b). The decision on the factors to retain was based on the results of a scree test and interpretability of the factors (Kim and Mueller 1978). The factor score for each pattern was computed by summing the observed variables multiplied with their factor loading. These scores were used to rank participants according to the degree to which they conformed to each dietary pattern. A linear model (Cohen and Cohen 1975) was used in the description of the data.

Dietary pattern scores and nutrient intakes were adjusted for total energy intake by the method described by Willet and Stampfer (1986) in Studies I, II and IV). Relative risks of type 2 diabetes with 95% confidence intervals between quartiles of pattern scores and dietary variables were calculated using Cox's life table regression model (Cox 1972). Potential confounding and effect modifying factors (age, body-mass index, energy intake, smoking, geographical area, and family history of diabetes) were entered into the model. Tests for trends through the quartiles were carried out based on a likelihood ratio test, treating all variables in the model as continuous by entering the quartile numbers. In further analyses the question of whether the dietary pattern approach can actually assess interaction between nutrients was explored by including the dietary pattern score variable in the same model simultaneously with its components (Study II). The effect on the risk estimate of the component included can be assessed by comparing the risk estimates between models with and without the component.

For this thesis the analyses were standardized so that the results presented in the same tables or figures are uniform and comparable with each other. The energy adjustment of the nutrients and the pattern scores was performed by a standard modeling method instead of the residual method. The results are based on the model including age, body-mass index, energy intake, smoking, geographical area, and family history of diabetes and in all analyses the follow-up period was defined as 23 years and the study population was 4304 persons.

5 RESULTS

This section summarizes the main findings of the original articles. The values presented in the tables and the figures in this summary are slightly different from the values presented in the original articles due to standardization of the method of handling of confounding, the follow-up period and the study population.

5.1 Description of the data

5.1.1 Dietary patterns

Through factor analysis of the whole dietary data with 10 054 observations, two factors, one labeled as the prudent pattern and the other as the concervative pattern, were revealed when factors with eigenvalues greater than 2.5 were retained (Study I). Other factors with eigenvalues less than 1.5 were discarded. The factor-loading matrix for these two retained dietary patterns is shown in Table 7. The factor labeled as prudent dietary pattern was characterized by consumption of fruits and vegetables. Other foods having weaker correlation with this prudent pattern were poultry, eggs, regular dairy (includes cheese, cream, ice-cream and yoghurt), berries, margarine and oil, reduced-fat dairy products (includes skimmed or low-fat milk, low-fat cheese) and frozen and canned fish. The factor labeled as conservative dietary pattern was characterized by butter, potato, whole milk, red meat, jams and sugar rich condiments, grains, processed meat, peas and nuts and salted, smoked and unprocessed fish. Of the plant foods, grains were correlated with the conservative pattern. Eggs, red meat and peas and nuts were correlated with both patterns, however, red meat seemed to have a stronger correlation with the conservative pattern.

Table 7. ***Factor loading matrix for the major dietary patterns identified from the Finnish Mobile Clinic Health Examination Survey (Study I)***

Foods or food groups[a]	Correlation coefficient (N= 10 054)	
	Prudent pattern	Conservative pattern
Yellow and red vegetables	0.64	-[b]
Green vegetables	0.63	-
Fruit	0.62	-
Vegetables, other	0.57	-
Poultry	0.35	-
Eggs	0.34	0.32
Regular dairy	0.26	-
Berries	0.28	-
Margarine and oil	0.26	-
Reduced-fat- dairy	0.26	-
Fish, canned or frozen	0.22	-
Butter	-	0.68
Potato	-	0.66
Whole milk	-0.30	0.59
Red meat	0.32	0.56
Jams and sugar rich condiments	-	0.49
Rye	-	0.45
Processed meat	-	0.43
Grain, other than rye or wheat	-	0.43
Wheat	-	0.39
Peas and nuts	0.23	0.30
Fish, salted or smoked	-	0.31
Fish, unprocessed	-	0.31

[a]The food groupings are presented in detail in appendix table 1.
[b]To simplify data presentation, loadings with absolute value less than 0.20 are not shown.

5.1.2 Associations between non-dietary and dietary factors and prudent dietary pattern

Baseline characteristics of the study subjects according to quartiles of the prudent dietary pattern scores are presented in Table 8. Persons having higher prudent dietary pattern scores were younger than persons with low prudent pattern scores and they were less likely to be men or smokers.

The prudent dietary pattern was directly associated with higher intakes of vitamin E, vitamin C, and carotenoids. Of the plant foods, intakes of vegetables, fruit and berries, peas and nuts were directly associated with the prudent pattern scores, whereas whole grain and potato intakes were inversely associated (Table 8). Other dietary components that were directly related with prudent pattern were processed and red meat and fish, poultry, margarines and oils, regular and reduced-fat dairy products (Study I).

Table 8. ***Mean values and distributions (%) of personal characteristics at baseline according to quartiles of prudent dietary pattern scores***

Variable	Quartile of prudent pattern scores							
	1 (Lowest)		2		3		4 (Highest)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age, years	53.1	± 8.2	52.5	± 8.2	51.4	± 7.8	50.6	± 7.8
Sex, %								
Men	30.5		25.0		22.3		22.2	
Women	18.8		25.0		28.1		28.1	
Family history of diabetes, %								
Yes	24.5		22.6		24.9		28.0	
No	25.1		25.6		25.0		24.3	
Current smokers, %								
Yes	29.1		24.1		23.1		23.6	
No	23.0		25.4		25.9		25.7	
Hypertension, %								
Yes	21.5		25.3		27.3		25.9	
No	25.7		24.9		24.6		24.8	
Serum cholesterol, mmol/L	6.9	± 1.4	7.0	± 1.5	7.1	± 1.4	7.0	± 1.4
Body mass index, kg/m^2	26.0	± 4.1	26.5	± 4.0	26.6	± 4.0	26.7	± 4.0
Nutrient intakes								
Energy, kcal /day	2525	± 817	2384	± 790	2478	± 827	2586	± 954
Total fiber, g/day	25.6	± 11.1	25.4	± 10.3	27.8	± 10.9	30.6	± 13.4
Cereal fiber, g/day	19.7	± 10.1	18.6	± 9.4	19.5	± 9.9	19.5	± 12.0
Vitamin E, mg /day[a]	6.1	± 2.2	6.4	± 2.4	7.3	± 2.7	9.2	± 4.3
Vitamin C, mg/day	50.7	± 19.7	61.0	± 21.3	78.9	± 24.2	112	± 44.5
Carotenoids, µg / day[b]	1978	± 1126	2822	± 1479	3995	± 2085	6372	± 3842
Food intakes, g/day								
Vegetables, all[c]	32.8	± 25.5	66.1	± 33.6	104	± 43.5	180	± 85.7
Yellow and red vegetables	19.6	± 20.0	39.3	± 29.2	60.4	± 38.3	102	± 66.8
Green vegetables	11.0	± 11.2	22.1	± 16.8	34.9	± 22.6	57.9	± 40.0
Vegetables, other	2.3	± 3.7	4.6	± 5.7	8.3	± 9.5	20.1	± 23.1
Potato	248	± 137	216	± 119	218	± 119	201	± 125
Peas and nuts	4.2	± 4.7	5.5	± 5.5	6.4	± 6.5	8.0	± 10.2
Fruit and berries	40.4	± 40.7	78.6	± 60.9	122	± 83.5	209	± 151
Whole grain[d]	204	± 112	180	± 102	183	± 102	176	± 118

[a]α-tocopherol equivalents.
[b]Sum of α-, β-, and γ-carotenes, lycopene, β-cryptoxanthin and lutein, and zeaxanthin.
[c]Excluding potato.
[d]The whole grain food group contained rye bread, rye crisp bread, and all whole grain flours and other products (rye, whole wheat, wheat germ, rolled oats, barley, millet, buckwheat) derived from different grain foods (e.g., porridge, gruel, Karelian pie).

5.1.3 Associations between non-dietary and dietary factors and diabetes

Persons who developed diabetes during the follow-up were older, more obese and more likely to be women or hypertensive but less likely to be current smokers. The cases more often had a family history of diabetes (Table 9). Age, sex, body-mass index and hypertension predicted increased risk of type 2 diabetes in these data (Study III). Of the dietary variables, persons with incident diabetes had lower mean intake of vegetables, fruit and berries and whole grain at baseline. They also had a smaller energy intake and their nutrient intakes were smaller (Table 9).

Table 9. ***Mean values and percentages of personal characteristics at baseline in occurred cases of type 2 diabetes and non-cases***

Variable	Cases (N=383)		Non-cases (N=3921)	
	Mean	SD	Mean	SD
Age, years	53.9	± 7.6	51.7	± 8.0
Sex, %				
Men	7.2		92.8	
Women	10.9		89.2	
Family history of diabetes, %				
Yes	12.1		87.9	
No	8.1		91.9	
Current smokers, %				
Yes	6.2		93.8	
No	10.2		89.8	
Hypertension, %				
Yes	17.3		82.7	
No	7.2		92.8	
Serum cholesterol, mmol/L	6.8	± 1.3	7.0	± 1.4
Body mass index, kg/m^2	29.7	± 4.5	26.2	± 3.8
Nutrient intakes				
Energy, kcal/day	2324	± 857	2510	± 850
Total fiber, g/day	25.0	± 11.1	27.6	± 11.7
Cereal fiber, g/day	17.4	± 10.0	19.5	± 10.4
Vitamin E, mg/day[a]	6.6	± 2.3	7.3	± 3.3
Vitamin C, mg/day	72.3	± 34.5	75.8	± 37.5
Carotenoids, µg / day [b]	3547	± 2839	3816	± 2897
Food intakes, g/day				
Vegetables, all[c]	88.3	± 73.5	96.5	± 76.2
Yellow and red vegetables	53.1	± 52.7	55.7	± 52.2
Green vegetables	27.2	± 26.6	31.9	± 30.9
Vegetables, other	8.0	± 12.8	8.9	± 14.8
Potato	215	± 120	221	± 127
Peas and nuts	5.6	± 6.1	6.0	± 7.3
Fruit and berries	106	± 96.1	113	± 114
Whole grain[d]	168	± 109	187	± 109

[a]α-tocopherol equivalents.
[b]Sum of α-, β-, and γ-carotenes, lycopene, β-cryptoxanthin and lutein and zeaxanthin
[c]Excluding potato.
[d]The whole grain food group contained rye bread, rye crisp bread, and all whole grain flours and other products (rye, whole wheat, wheat germ, rolled oats, barley, millet, buckwheat) derived from different grain foods (e.g., porridge, gruel, Karelian pie).

5.2 Follow up analyses

5.2.1 Prudent dietary pattern and risk of type 2 diabetes (Top-level association, Study I)

During the 23-year follow-up higher prudent pattern scores at baseline predicted a lower risk of type 2 diabetes. When the highest and the lowest quartiles of the prudent pattern scores were compared the relative risk of type 2 diabetes was 0.72 (95% confidence interval (CI) = 0.53–0.97; P for trend (P) = 0.05), after adjustment for age, sex, body mass index, energy intake, smoking, geographical area, and family history of diabetes (Figure 1). Relative risks across the quartiles of the prudent dietary pattern scores are presented in Appendix Table 2.

No significant interactions were found when the possible modifying effect of potential interacting variables such as age, sex, body-mass index and smoking were analyzed (Study I). A twice as high risk of type 2 diabetes was observed among persons with a low prudent pattern score and high conservative pattern score compared with persons with low scores in both dietary patterns (Study I).

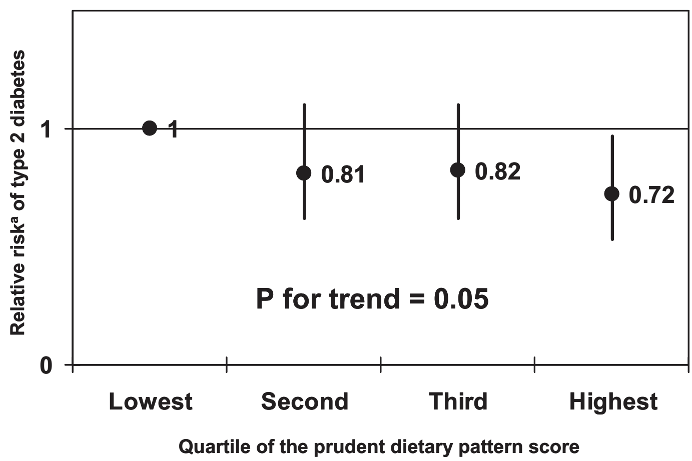

Figure 1. ***Relative risk and 95% confidence interval of type 2 diabetes between quartiles of prudent dietary pattern scores. [a]Adjusted for age, sex, body mass index, energy intake, smoking, geographical area, and family history of diabetes***

5.2.2 Vegetables, fruit and berries and whole grain and risk of type 2 diabetes (Intermediate-level associations, Studies II and III)

Of the components of the prudent dietary pattern, the consumption of vegetables, green ones, especially and fruit and berries was associated with a reduced diabetes risk when adjusted for age, sex, energy intake and body-mass index (Study II). Further adjustment for geographical area, smoking and family history of diabetes tended to attenuate the observed association. However, the inverse association between the consumption of green vegetables and diabetes risk and fruit and berries and diabetes risk remained significant (Figure 2). Relative risks between the highest and lowest quartiles of consumption were 0.69 (95% confidence interval (CI) = 0.50–0.93; P for trend (P) 0.02) for green vegetables, and 0.69 (CI = 0.51–0.92; P = 0.03) for fruit and berries when adjusted for age, sex, body-mass index, energy intake, smoking, geographical area, and family history of diabetes. Intake of potato was associated with an increased risk of type 2 diabetes (RR = 1.42; CI = 1.02–1.98; P = 0.03) when adjusted for age, body-mass index, energy intake, smoking, geographical area, and family history of diabetes.

Although grain was not a component of the prudent dietary pattern (Table 7), whole grain was included in the study for intermediate-level associations as a food of plant origin. An inverse gradient between consumption of whole grain and the incidence of type 2 diabetes was observed during follow-up of 10 years (Study III). However, extension of the follow-up to 23 years attenuated the association. Relative risk between the extreme quartiles of whole grain consumption was 0.88 (CI = 0.63–1.23; P = 0.18) when adjusted for age, body-mass index, energy intake, smoking, geographical area, and family history of diabetes (Figure 2).

No significant interactions between food intake and age, sex, body-mass index, or smoking and type 2 diabetes risk was found (data not shown). Consumption ranges, as well as the relative risks across the quartiles of the consumption of plant foods, are presented in Appendix Table 2.

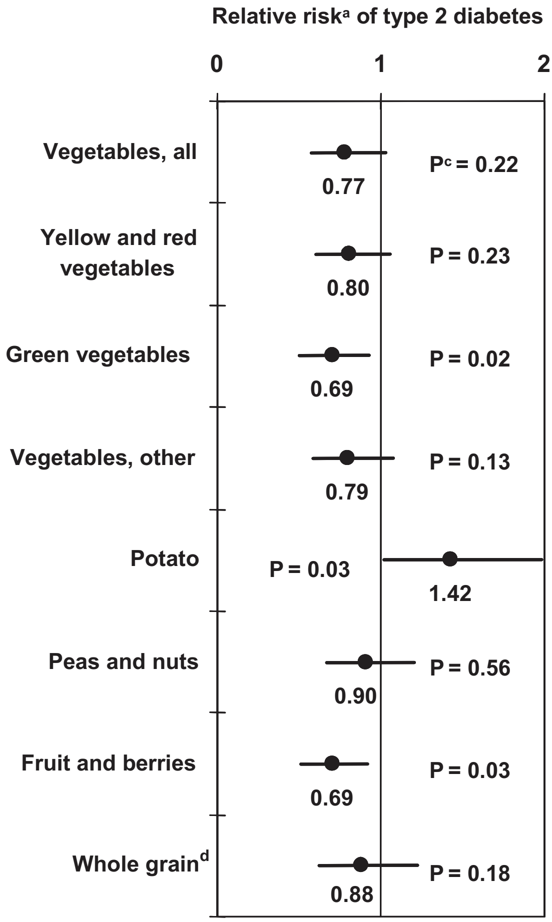

Figure 2. ***Relative risk and 95% confidence interval of type 2 diabetes between the extreme quartiles of individual plant foods.*** [a]***Adjusted for age, sex, body mass index, energy intake, smoking, geographical area, and family history of diabetes.*** [b]***Excluding potato.*** [c]***P value for trend.*** [d]***The whole grain food group contained rye bread, rye crisp bread, and all whole grain flours and other products (rye, whole wheat, wheat germ, rolled oats, barley, millet, buckwheat) derived from different grain foods (e.g., porridge, gruel, Karelian pie)***

5.2.3 Dietary fiber and antioxidant vitamins and risk of type 2 diabetes (Bottom-level associations, Studies III and IV)

Dietary fiber and risk of type 2 diabetes

An inverse association between intake of fiber, especially insoluble noncellulose polysaccharides and cereal fiber, and the incidence of type 2 diabetes was observed during follow-up of 10 years (Study III). Although, the extension of the follow-up to 23 years tended to attenuate the associations, they remained significant: for total fiber intake the relative risk between the extreme quartiles was 0.66 (95% CI = 0.45–0.97; P = 0.02), after adjustment for age, sex, body-mass index, energy intake, smoking, geographical area, and family history of diabetes (Figure 3). The corresponding value of insoluble noncellulose polysaccharides was 0.67 (95% CI = 0.46–0.98; P = 0.04) and of cereal fiber was 0.69 (95% CI = 0.47–1.00; P = 0.04). Of fiber provided by different food groups, cereal fiber, but not the fiber from vegetables or fruits, was significantly associated with the risk of type 2 diabetes (Figure 3, Appendix Table 2).

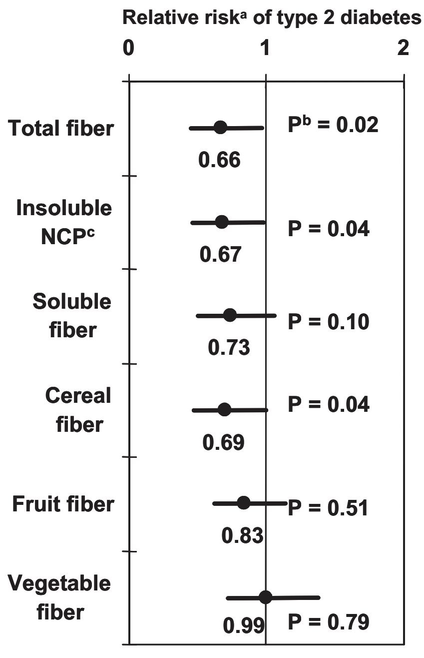

Figure 3. ***Relative risk and 95% confidence interval of type 2 diabetes between the extreme quartiles of intakes of total fiber and fiber components. [a]Adjusted for age, sex, body mass index, energy intake, smoking, geographical area, and family history of diabetes. [b]P value for trend. [c]Noncellulose polysaccharides***

Dietary antioxidant vitamins and risk of type 2 diabetes

Intakes of vitamin E, and carotenoids but not intake of vitamin C, were inversely associated with the risk of type 2 diabetes (Figure 4). The relative risk of type 2 diabetes between the extreme quartiles of vitamin E intake was 0.68 (CI = 0.47–1.00; P = 0.14), and between the extreme quartiles of carotenoids it was 0.69 (0.51–0.93; P = 0.14) when adjusted for age, sex, body-mass index, energy intake, smoking, geographical area, and family history of diabetes. Intake ranges as well as relative risks across the quartiles of the intakes of antioxidant vitamins are presented in Appendix Table 2.

Of the individual tocopherols and tocotrienols, intakes of α-tocopherol, γ-tocopherol, δ-tocopherol and β-tocotrienol were associated with a reduced risk of type 2 diabetes, whereas, of the carotenoids considered, β-cryptoxanthin showed an inverse association with risk of type 2 diabetes (Study IV).

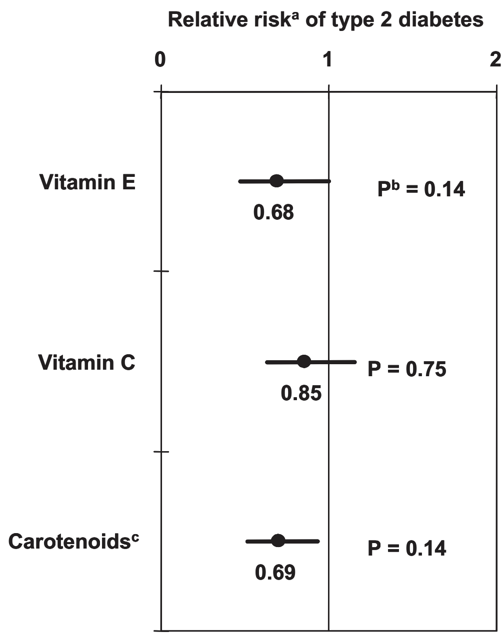

Figure 4. ***Relative risk and 95% confidence interval of type 2 diabetes between the extreme quartiles of antioxidant vitamins. [a]Adjusted for age, body mass index, energy intake, smoking, geographical area, and family history of diabetes. [b]P value for trend. [c]Sum of α-, β-, and γ-carotenes, lycopene, β-cryptoxanthin and lutein, and zeaxanthin***

5.2.4 Exploration of synergy between components of the prudent dietary pattern

The advantage of the pattern analysis is that the presence of the potential synergistic effect between single foods and nutrients can be accounted for. The top-down strategy includes exploration of potential synergy between smaller units accounted by the larger unit. To investigate whether the components of the prudent dietary pattern accounted for the effect observed for the pattern, the contribution of the components that were related to the pattern and diabetes risk were evaluated by adding those to the model simultaneously with the dietary pattern scores (Study II). The addition of each of the components of the prudent pattern attenuated the association between the prudent dietary pattern and diabetes risk. Finally, in a model including intakes of plant origin food items such as fruit, berries, green vegetables and margarine and oil, the predictive value of the prudent dietary pattern was entirely explained by these foods (Study II). After inclusion of green vegetables, fruit and berries, and margarine and oil, the relative risk of type 2 diabetes between the extreme quartiles of the prudent pattern scores was 0.97 (CI = 0.63–1.49; P > 0.99) when adjusted for age, sex, body-mass index, energy intake, smoking, geographical area, and family history of diabetes.

Of the nutrients derived from plant foods, inclusion of dietary fiber, vitamin E, vitamin C, β-carotene and folic acid in the model with the prudent pattern considerably weakened the inverse association observed for the prudent pattern (Study I). After inclusion of vitamin E, vitamin C , carotenoids and dietary fiber, the relative risk of type 2 diabetes between the extreme quartiles of the prudent pattern scores was 0.81 (CI = 0.52–1.28; P = 0.39) when adjusted for age, sex, body-mass index, energy intake, smoking, geographical area, and family history of diabetes. The top-level association was thus totally explained by the intermediate-level and bottom-level factors.

6 DISCUSSION

6.1 Study population

Subjects of the study were drawn from the Finnish Mobile Clinic Health Examination Survey carried out by the Social Insurance Institution during the period 1966–1972. The baseline examinations were carried out in 34 rural, industrial or semiurban populations in six regions of the country and the study population consisted of more than 50 000 persons aged 15 or older (Aromaa 1981). On average, the participation rate was good (81.9% of men and 83.2% of women participated in the examination), but subjects over 70 years of age were under-represented mainly because of chronic illness (Aromaa 1981). Thus, the study population was not completely representative of the whole Finnish population. However, this under-representation of the oldest age-group is not a disadvantage, because of the etiological nature of the study and exclusion of persons over 69.

6.2 Methods

6.2.1 Dietary methods

Measurement of dietary data requires an appropriate instrument to collect the information on the use of food items of interest. In the present study, the dietary data were collected using a 12-month dietary history interview. Although the dietary history interview is considered relatively accurate, certain inaccuracies in the method tend to affect the associations observed between dietary exposure and outcome (Willett 1998). The result of the dietary history interview is always a subjective assessment of the respondent's own dietary habits. A period of 1 year is a lengthy time to recall. Food models were used to diminish errors in recall, and open-ended questions enabled respondents to be more specific in their answers. To minimize possible bias caused by the differences between the interviewers, trained nutrition professionals employed structured questionnaires (Järvinen 1996).

Short-term repeatability of the dietary history method was relatively good (Järvinen et al. 1993a). Long-term repeatability was poorer. The poorer long-term consistency can be partly explained by changes in Finnish dietary habits. It has been found that butter consumption decreased, low-fat milk replaced whole milk and fruit and vegetable consumption increased during a 10-year period from 1972 to 1982 (Pietinen et al. 1988). According to balance sheets for food commodities consumption, of grain products has been constantly decreasing from the sixties to the end of nineties (Ministry of Agriculture and Forestry 2003)

Among the Finnish Mobile Clinic Survey population, vitamin E intake has been found to be related to serum α-tocopherol concentration (Knekt et al. 1988). Dietary β-carotene was associated with serum concentrations in women, but not in men (Järvinen et al. 1993b). It is possible that the lower agreement in men is due to the erosive effect of smoking on β-carotene status. Hence, it can be considered that dietary intakes of antioxidant vitamins reflected circulating antioxidants available for tissue cells in women, but in men the available amount may be overestimated.

6.2.2 Food composition values

Food composition values used in this study were mainly drawn from Finnish food composition tables (Rastas et al.1989) completed with other analyzed values of foods available in Finland. It is difficult to estimate how well the analyzed values of the food samples collected in the eighties are in agreement with the actual food composition at the baseline of the present study. As far as carotenoids and tocopherols and tocotrienols are concerned, specific analytical methods for measuring these components only became available during the eighties. In addition to changes in nutrient composition of foods over time and food preparation techniques, the nutrient composition tables are constantly being developed. Consequently, ranking according to intakes is commonly used in epidemiologic analyses. In such an approach, the validity of the results depends on the accuracy of the ranking instead of absolute intake levels. The participants in the present study were similarly ranked for their β-cryptoxanthin intake (Montonen et al. 2004) using either the values from the study of Heinonen (1990), or the further developed (Brugård Konde et al. 1996; O'Neill et al. 2001) β-cryptoxanthin values.

In the present study, the nutrient contents of the foods referred to raw foodstuffs. Because losses during food preparation are not accounted for, the intakes of certain vitamins have been overestimated. In particular, the vitamin C content in food may greatly decrease during cooking. On the other hand, cooking may even increase the bioavailability of carotenoids (van het Hof et al. 1999; Edwards et al. 2002)

6.2.3 Recognition of diabetes cases from the register

The information on incident diabetes was obtained from a nationwide register of drug reimbursements (Reunanen et al. 1998). The register does not include persons with diabetes undergoing dietary therapy only, which may have led to conservative estimates of the strength of the associations between dietary variables and diabetes risk. In the Health 2000 Survey, 23% of men and 38% of women with diabetes did not have medication for diabetes (Reunanen et al. 2004), suggesting that the number of missed cases is relatively large. However, the persons with diabetes treated by diet only often have a mild form of the disease. Thus, restricting the cases to those needing drug treatment reinforces the validity and more serious nature of their disease.

The validity of the method of identifying cases of diabetes via the nationwide registry of drug reimbursement depends mainly on the number of false positive patients. These false positive cases have been eliminated by double checking the detailed certificate of the diagnosis from a physician enclosed with the application for drug reimbursement. According to The Social Insurance Institution's records, the drug registry covers over 90% of persons having medical treatment for type 2 diabetes (Social Insurance Institution 2003). Hence, the validity of the diabetes cases obtained from the register of drug reimbursement is relatively good. However, the limited statistical power due to the potentially large number of missed cases on diet therapy is a limitation in this study.

6.2.4 Consideration of the energy adjustment of the nutrients and pattern scores

The residual method described by Willett and Stampfer (1986) was applied to adjust nutrient intakes as well as pattern scores for energy intake in the original articles I, II and IV. This method is commonly used to reduce extraneous variation or confounding due to variation in body size, physical activity, or metabolic efficiency or caused by over or under-reporting. However, this adjustment procedure may introduce attenuation bias in the diet-disease association unless total energy intake is entered in the model (Palmgren and Kushi 1991). It has also been shown that simultaneous inclusion of the energy adjusted nutrient and total energy intake as covariates in the model will result in the same model fit, β-coefficients and standard errors as inclusion of crude nutrient intake and total energy intake (Pike et al. 1989; Palmgren and Kushi 1991). Since similar results have been produced by both methods, either by the residual method with energy intake simultaneously in the model or by the standard multivariate method, the standard multivariate method was used to adjust for energy intake for sake of simplicity in the analyses carried out for this thesis.

6.3 Plant foods and risk of type 2 diabetes

6.3.1 Top-level associations

Two dietary patterns were identified and labeled as the 'prudent' pattern and the 'conservative' pattern. Since food consumption patterns reflect existing preferences and the foods available, it might be expected that the identified patterns differ according to population and time. However, the major dietary patterns observed among Finns in 1967–1972 have similarities to those observed in the 1980s and 1990s in the USA, Denmark, and Sweden (Hu et al. 1999b; Fung et al. 2001b; Osler et al. 2001; Terry et al. 2001). In the present study, the prudent dietary pattern was characterized by fruit, vegetables and poultry which were associated with a prudent or vegetable-rich pattern in these previous studies.

The prudent dietary pattern, characterized most dominantly by fruit and vegetables, was inversely associated with incidence of type 2 diabetes. The findings corroborate the previously reported results of the Health Professionals Follow-up Study and the Nurses' Health Study (van Dam et al. 2002a; Fung et al. 2004) in which the prudent dietary pattern (rich in vegetables, fruit, fish, poultry, and whole grains) suggested a reduced risk of type 2 diabetes during 12 year follow-up.

The result is also somewhat in line with a study based on the data from the Nurses' Health Study in which an *a priori*-formed pattern score based on the intake of cereal fiber, polyunsaturated fat, *trans*-fatty acids, and postprandial glycemic load was related to the risk of developing diabetes during a 16-y follow-up (Hu et al.2001b).

6.3.2 Intermediate-level associations

In the present study, consumption of green vegetables, fruit and berries were inversely associated with risk of type 2 diabetes, whereas potato consumption was directly associated. The results from previous studies on fruit and vegetables and the risk of type 2 diabetes have been inconclusive (Table 2). The finding on green vegetables is in line with the results from previous cross-sectional studies showing an inverse association between intake of leafy green vegetables and blood glycated hemoglobin level (Sargeant et al. (2001).

In the present study, the relation between the prudent pattern and diabetes risk was completely explained by its intermediate-level dietary components, suggesting that no food synergy was carried by the pattern and that the pattern actually summarizes the effects of individual foods or food groups. Alternatively, the results suggest that potential non-dietary factors beyond the prudent pattern possibly have a parallel effect with the analyses of individual foods.

Potato consumption was associated with an increased risk of diabetes. Abundant consumption of potato may by linked to diabetes development through a mechanism related to increased post-prandial glucose levels, although the glycemic index of potato depends largely on the strain and the method used in preparation (Foster-Powell and Miller 2002). Although potatoes are often included in the same group as vegetables, some studies have presented the results separately for potatoes. In previous cohort studies, intake of potatoes did not differ between diabetes cases and non-cases (Lundgren et al. 1989) nor was it associated with glucose intolerance (Feskens et al. 1991; Feskens et al. 1995). In one cross-sectional study, frequent potato consumption was associated, but non-significantly, with a higher risk of type 2 diabetes (Williams et al. 1999). In the present study, potato was consumed as cooked or mashed potatoes as a staple food. When comparing the results of the present study with other previous studies it should be borne in mind that the way potato is consumed differs according to population and time.

Consumption of whole grain was inversely associated with the risk of type 2 diabetes in the present study (Study III). This finding is in line with previous studies mainly from the USA, which reported a reduced type 2 diabetes risk at higher levels of whole grain consumption (Liu 2003a). In the present study, whole grain consumption consisted mainly of rye bread, whereas in previous USA studies whole grain consumption referred mainly to whole wheat or other grains (Meyer et al. 2000; Liu et al. 2000). In Finnish intervention studies, whole-meal rye bread has been shown to produce a lower insulin response than refined wheat bread (Leinonen et al. 1999; Juntunen et al 2002). However, among post-menopausal women the acute insulin response increased significantly more during the rye-bread period than during the wheat-bread period (Juntunen et al. 2003b).

6.3.3 Bottom-level associations

Fiber

Whole grain, most importantly rye, is a major source of dietary fiber for Finns. Accordingly, an inverse relationship between intake of total fiber, especially cereal fiber, and type 2 diabetes risk was found. Persons with higher cereal fiber intake had a 30% lower risk of type 2 diabetes than the persons in the lowest intake category. The result on cereal fiber corroborates earlier cohort studies that have suggested a lower risk of type 2 diabetes among persons with a higher level of cereal fiber intake (Table 4).

According to biological mechanisms that have been hypothesized, the beneficial effect of soluble fiber may be mediated through slow absorption and digestion of carbohydrates leading to a reduced insulin demand (Anderson et al. 1979; Slavin et al. 1999), whereas insoluble fiber shortens intestinal transit time, which therefore allows less time for carbohydrates to be absorbed (Anderson et al. 1979).

In the present study, fiber from vegetables or fruits was not associated with diabetes risk. The result is in line with previous studies that have assessed the diabetes risk by different fiber components (Salmeron et al. 1997a; Salmeron et al. 1997b; Meyer et al. 2000; Stevens et al. 2002). Thus, it seems conceivable that the potential preventive effect of fruits and vegetables is mediated by other components than dietary fiber.

Antioxidant vitamins

In the present study, the intakes of vitamin E and total carotenoids were associated with a reduced risk of type 2 diabetes. These results add strength to the hypothesis that intake of antioxidant vitamins plays a role in type 2 diabetes prevention (Slonim et al.1983; Murthy et al. 1992). Risk of type 2 diabetes was 30% lower among persons in the highest quartile of vitamin E intake. The result is in line with the results from previous follow-up studies suggesting an inverse association between dietary and serum α-tocopherol and incidence of type 2 diabetes (Salonen et al. 1995; Mayer-Davis et al. 2002). In clinical experiments, pharmacological doses of vitamin E have improved insulin mediated glucose uptake (Paolisso et al.1993a; Paolisso et al. 1993b Paolisso et al. 1994a). Previous epidemiological evidence on carotenoids and the development of diabetes relies mainly on cross-sectional studies that have rather inconsistent results (Table 6). Supplementation of β-carotene showed no effect on diabetes risk in a long-term supplementation trial among US male physicians (Liu et a. 1999).

The present study does not support previous prospective (Feskens et al. 1995) and some cross-sectional studies (Shoff et al. 1993; Boeing et al. 2000; Sargeant et al. 2000) which have linked vitamin C to better glucose metabolism. The controversial result may be due to rather low mean vitamin C intake in Finland at the time of the baseline. Since potatoes probably contributed heavily to the vitamin C intake in these data (Koskinen 1975), the vitamin C result is apparently confounded by the potato intake.

Vitamin E is the most efficient chain-breaking antioxidant that protects tissue membranes from oxidative damage (Halliwell and Gutteridge 1989). Vitamin C has the ability to regenerate tocopherols and tocotrienols from tocopheroxyl or tocotrionoxyl radicals (Frei et al. 1989). It has also been postulated that carotenoids may form part of the antioxidative mechanism of cells, acting as antioxidants or modifying the levels of other antioxidants (Palozza and Krinsky 1992). According to these facts it seems plausible that the beneficial effects related to antioxidants could be enhanced by the synergy between varieties of antioxidants and other nutrients present (Liu 2003b). The possible protective effects of vegetables and fruits resulting from the combined action of some antioxidant cocktail has been suggested as a possible reason for the controversial results between supplementation interventions and observational studies on the health effects of antioxidants.

In the present study, the observed association between the prudent dietary pattern and reduced risk of type 2 diabetes was totally explained by its components and furthermore by nutrients provided by the plant foods. This result suggests that the preventive effect of the interactions between nutrients does not exist or it cannot be revealed using the dietary pattern approach. However, factors other than dietary antioxidants or fiber may also explain the bottom-level findings. It is possible that individuals with diets high in antioxidant vitamins or fiber in the 1970s have since had healthier lifestyles than other persons. They may be more physically active and more educated and therefore more health conscious than others. It is also possible that the inverse association may be explained by factors related to better socioeconomic status.

6.3.4 Consideration of the effect of follow-up time

Length of follow-up plays a crucial role when results of prospective studies are interpreted. A great advantage of a long follow-up is that a higher number of incident cases can be obtained. However, the risk estimates tend to move towards unity during long follow-up, since a longer follow-up period allows more changes to appear in the rate of exposure. Accordingly, the extension of the follow-up from 10 to 23 years weakened the associations observed in Study III. In the previous follow-up studies on intakes of whole grain and fiber, the incidence of type 2 diabetes has been assessed during follow-up of 6 to 12 years (Tables 3 and 4).

The effect of changes in exposure during follow-up can be reduced by shortening the follow-up period. However, a major disadvantage in this method is that the lower number of incident cases during shorter follow-up reduces statistical power. For this reason the use of longer follow-up was justified in this thesis.

The effect of the pre-clinical phase of the disease can be accounted for by excluding a few of the first years from the follow-up. As the disease is mostly symptom free, changes in food consumption due to developing disease are probably scarce. Accordingly, in the present study the results did not vary when the first two years were excluded suggesting that the results are not affected by the pre-clinical phase of the disease (Study III).

6.3.5 Confounding factors

The relationship between intake of plant foods and incidence of type 2 diabetes may be an effect of the nutrients used or it may be a result of confounding due to other factors related to plant food consumption. According to epidemiologic literature, obesity, physical inactivity, higher age, family history of diabetes, high blood pressure, higher levels of cholesterol, alcohol intake, and smoking are the main risk factors for type 2 diabetes. Potential confounding was handled by adjusting the effect by entering the potential confounding factor into the model. The effect of the included variable can be observed by comparing the risk estimates between models. The results in top-level, intermediate-level and bottom-level analyses were independent of the factors related to lifestyle, since the inclusion of the lifestyle factors in the model had a very limited effect on the results. It is, however, possible that some residual confounding has remained after adjustments due to inaccurate measurement of smoking status or blood pressure.

In addition to lifestyle factors, many dietary factors appear to be confounders when the nutrients are studied, due to their similar food sources. The preventive effect observed for plant foods as well as antioxidant vitamins and fiber may be mediated by several other nutrients. Besides antioxidant vitamins and fiber, plant food products are a good source of several vitamins, minerals, unsaturated fat, phytoestrogens and phenolic compounds (Prior 2003; Slavin 2004). Magnesium (derived mainly from grains) has been related with reduced diabetes development since hypomagnesemia may impair insulin secretion and promote insulin resistance. An inverse relationship between magnesium intake and type 2 diabetes risk has been shown in prospective studies (Salmeron et al.1997a; Meyer et al.2000). Flavonoids (derived mainly from onions, apples, citrus fruits and berries) have been found to be related to a reduced incidence of type 2 diabetes (Knekt et al. 2002). Also folic acid (derived mainly from fruits, vegetables and whole-grain) and pyridoxine (derived mainly from grains, pulses and nuts) have a potential reducing effect on the development of type 2 diabetes through a lower concentration of serum homocysteine (Boushey et al.1995). Type of fat has also been related to incidence of diabetes (Hu et al. 2001c).

In the present study, the inverse association of cereal fiber consumption on diabetes risk was apparently not completely due to higher intake of antioxidant vitamins, vitamin B6, folic acid, or magnesium, or lower intake of saturated fatty acids, since adjustment for these nutrients did not alter the results (Study III). The inverse association between the antioxidant vitamins and risk of type 2 diabetes was independent of the intakes of saturated fat, pyridoxine, folic acid, flavonoids, and cereal fiber (Study IV). Therefore, it appears conceivable that the beneficial effect associated with intakes of antioxidant vitamins and cereal fiber against development of type 2 diabetes could be ascribed to factors specifically related to cereal fiber and antioxidants.

Unfortunately, as an apparent limitation of the present study, no valid data on baseline physical activity was available. Since persons with healthier diets may be physically more active than other persons, the lack of physical activity data in particular may have confounded the results. Physical activity has been consistently associated with decreased risk of type 2 diabetes (van Dam 2003) by increasing insulin sensitivity (Soman et al. 1979). It is possible that high physical activity due to farm work has been associated with an energy rich conservative dietary pattern in the rural population in Finland at the time of the baseline. On the other hand, high leisure-time physical activity could be associated with a prudent dietary pattern. Another methodological issue is that numerous statistical tests were carried out and the probability of chance findings was increased accordingly.

The contribution of vitamin supplements was not considered here. The high proportion of individuals with dietary intake higher than the potential range of biological relevance may mask the effect of antioxidants from foods. Since the use of vitamin supplements was rare at the time of baseline (Klaukka et al. 1990), it is apparent that supplement use has not caused misclassification of nutrient intakes. It is not yet completely clear either, whether pharmacological doses of antioxidants have an effect on diabetes development.

6.3.6 Effect modification

Among free living persons exposure to factors inducing diabetes may vary in different populations and living circumstances. For example, women may be more prone to develop diabetes than men because of pregnancy; especially if they have had gestational diabetes. Smoking may decrease the available antioxidant capacity in the circulation. In the present study the association between plant foods and diabetes risk was studied within categories of age, sex, body-mass index and smoking. With the exception of smoking habits, the findings on negative association between the prudent dietary pattern and diabetes risk appeared to be more pronounced in persons with higher diabetes risk: older persons, women, and among individuals with higher body-mass index. However, all interaction terms were non-significant (Study I). No significant interactions between individual food items and age, sex, body-mass index, or smoking in predicting diabetes risk was found, suggesting that the results are not modified by these factors. However, the non-significance of the interaction terms may be due to limited statistical power.

6.4 Conclusions and directions for future research

The prudent dietary pattern mainly characterized by consumption of fruits and vegetables observed among Finns in 1967–1972, predicted a reduced risk of type 2 diabetes. In further analyses the association between the prudent pattern and diabetes risk was completely explained by intakes of fruit, berries, vegetables, and oil and margarine, suggesting that the pattern actually summarizes the effects of individual foods rather than carrying additional information due to potential interactions of dietary components. However, the possibility that potential non-dietary factors beyond the prudent pattern may have contributed to the result cannot be excluded.

The main hypotheses relating dietary fiber and antioxidants with prevention of type 2 diabetes were supported by this study. Dietary fiber, especially cereal fiber and several antioxidant vitamins were inversely associated with the risk of type 2 diabetes. Alternatively, the inverse association may be due to other bioactive compounds found in plant foods, such as minerals and phytoestrogens or by a lower glycemic index. Although these results and findings of the few other prospective studies seem promising, large-scale prospective studies and intervention trials are needed to establish firm conclusions.

The results of the present study point to the importance of dietary factors in the prevention of type 2 diabetes. However, the relative importance of diet and other lifestyle factors such as physical activity and obesity is not straightforward. In the present study as well as several previous ones physical activity was not taken into account in the analyses. Physical activity is probably an important confounding factor since prudent dietary habits may be associated with a higher level of leisure-time physical activity, and a conservative dietary pattern may be associated with heavy work at the time of the baseline of the present study. The results of the present study, like the findings of most previous studies, were independent of the baseline body-mass index. However, it is possible that some persons with a higher consumption of plant foods have survived without developing type 2 diabetes because of avoidance of weight gain during the follow-up period. On the other hand, it is possible that previous findings on the beneficial effects of lifestyle modifications aimed at prevention of type 2 diabetes (Pan et al. 1997; Tuomilehto et al. 2001; Knowler et al. 2002) are partly explained by dietary factors due to changes in dietary habits that come closer to a prudent diet. However, the overall proportion of the effect attributed to individual dietary factors apart from the major risk factors is still unknown and presents a major challenge for future research.

7 SUMMARY

B a c k g r o u n d

Prevalence of diabetes is rising rapidly in Finland. Obesity and low levels of physical activity are the most potent risk factors for type 2 diabetes. Besides these factors, several biological hypotheses link plant foods with the prevention or inhibition of the development of type 2 diabetes. However, epidemiological evidence on dietary factors in the prevention of type 2 diabetes is still incomplete.

O b j e c t i v e

This study was undertaken to explore the relationship between consumption of plant foods and nutrients derived from plant foods and the incidence of type 2 diabetes. More specific objectives were: 1) to identify major dietary patterns in representative data on Finns and to study whether the incidence of type 2 diabetes can be predicted by dietary pattern characterized by plant foods, 2) to study whether consumption of individual plant foods predicts the incidence of type 2 diabetes, 3) to test the fiber and antioxidant hypotheses that relate plant foods to prevention of type 2 diabetes, 4) to explore the extent to which the individual foods of the identified dietary patterns accounted for the associations observed.

P o p u l a t i o n

The study population was derived from the population-based data in the Finnish Mobile Clinic Health Examination Survey, carried out during the period 1966–1972. The dietary data of 10 054 participants were collected since 1967. After including only individuals aged 40–69 and free of diabetes, and excluding those who reported a daily energy intake of less than 800 or more than 6 000 kcal and who were pregnant, the final study population comprised 4304 persons. During a 23-year follow-up, a total of 383 incident cases of type 2 diabetes were identified by unique social security code from the registry of drug reimbursement kept by the Social Insurance Institution of Finland.

D i e t a r y m e t h o d s

Total habitual food consumption during the previous year was estimated, using a dietary history interview (Järvinen 1996). Interviewers used a questionnaire form listing over 100 food items and mixed dishes common in the Finnish diet. Several questions were open-ended and left the respondent an opportunity to specify answers and give further details during the interview. Food models were used to reduce errors of recall in regard to portion size. Consumption of foods was estimated

per day, week, month, or year according to the choice of the respondent. Individual consumption of food items and mixed dishes was converted to grams per day. The ingredients of mixed dishes were broken down into their components using a recipe file and daily intakes of energy and nutrients over all food items were calculated.

The food composition values were derived from Finnish food composition tables (Rastas et al. 1989). Food composition data on fiber, fatty acids, vitamin E and carotenoids and flavonoids were completed utilizing analyzed values of foods from other sources.

Non-dietary methods

A premailed questionnaire checked during the examination provided information about several demographic factors and health-behavior related habits such as occupation, current pregnancy, smoking, previous and current illnesses, and consumption of medicines, and general health status. Body-mass index was calculated on the basis of measured height and weight, and blood pressure was measured by the auscultatory method. Serum cholesterol concentration was determined with an autoanalyzer modification of the Liebermann-Burchard reaction. An oral glucose tolerance test was also performed.

Statistical methods

Factor analysis was used to identify dietary patterns (Kim and Mueller 1978). These scores were used to rank participants according to the degree to which they conformed to each dietary pattern. A linear model (Cohen and Cohen 1975) was used to estimate the associations between the dietary intakes and their determinants.

Relative risks of type 2 diabetes with 95% confidence intervals between quartiles of dietary variables were calculated using Cox's life table regression model (Cox 1972). Potential confounding and effect modifying factors (age, body-mass index, energy intake, smoking, geographical area, and family history of diabetes) were entered into the model. Tests for trends through the quartiles were carried out based on a likelihood ratio test, treating all variables in the model as continuous by entering the quartile numbers. The question of whether a possible additional effect of the dietary pattern score variables exists, besides the individual dietary variables, was explored by simultaneous inclusion of the dietary variables in a model including the pattern score variable.

Results

Two major dietary patterns were identified. The pattern labeled 'prudent' was characterized by higher consumption of fruit, berries and vegetables, and the pattern labeled 'conservative' by consumption of butter, potatoes, and whole milk. The prudent dietary pattern was associated with a reduced risk of type 2 diabetes. Of the components of the prudent pattern, higher intakes of green vegetables, fruit and berries, oil and margarine predicted a reduced risk of type 2 diabetes. Further analyses also revealed that the relation between the prudent pattern and diabetes risk was completely explained by these foods representing important components of the prudent dietary pattern, suggesting that the pattern actually summarizes the effects of individual foods or food groups rather than carrying further information on food synergy. Whole grain consumption was associated with a reduced risk of type 2 diabetes mellitus during 10 years of follow-up. However, the association became non-significant after extending follow-up to 23 years.

Two major hypotheses linking plant foods with a reduced risk of type 2 diabetes were tested. Of the dietary antioxidants, intake of vitamin E, as well as intake of total carotenoids was significantly associated with a reduced risk of type 2 diabetes. Of the individual tocopherols and tocotrienols, intakes of α-tocopherol, γ-tocopherol, δ-tocopherol and β-tocotrienol were associated with a reduced risk of type 2 diabetes, whereas, of the carotenoids considered, β-cryptoxanthin showed an inverse association with risk of type 2 diabetes. No association was evident between intake of vitamin C and type 2 diabetes risk. Dietary fiber, especially cereal fiber, intake was associated with a reduced risk of type 2 diabetes mellitus.

Conclusions

It seems conceivable that prevention of type 2 diabetes can be aided by consumption of plant foods, which are rich in nutrients with hypothesized benefits in the prevention of diabetes. The hypothesis on nutrients from plant foods on prevention of type 2 diabetes was supported as intakes of cereal fiber and antioxidant vitamins predicted reduced risk of type 2 diabetes mellitus. However, more studies are needed to consider whether the inverse association between plant food consumption and diabetes is mediated by hypothesized nutrients or other components from plant foods, or by lifestyle and sociodemographic factors related to dietary patterns.

8 YHTEENVETO

8.1 Johdanto

T a u s t a

Aikuistyypin diabeteksen esiintyvyys kasvaa voimakkaasti väestössämme. Lihavuus ja vähäinen fyysinen aktiivisuus ovat aikuistyypin diabeteksen tärkeimmät vaaratekijät. Näiden tekijöiden lisäksi diabeteksen ehkäisyyn tai kehittymisen hidastumiseen on liitetty useita ravintoon liittyviä hypoteesejä. Kuitenkin näyttö näiden merkityksestä aikuistyypin diabeteksen kehittymisessä on vielä puutteellista.

T a v o i t e

Tutkimuksen tavoitteena oli selvittää kasvikunnan tuotteiden käytön ja niiden sisältämien antioksidantti vitamiinien sekä ravintokuidun saannin yhteyttä aikuistyypin diabeteksen ilmaantuvuuteen. Erityisesti oli tarkoitus 1) selvittää suomalaisten ruokakäyttäytymistä sekä tutkia miten se ennustaa aikuistyypin diabeteksen ilmaantuvuutta, 2) tutkia ennustaako kasvisten, hedelmien ja marjojen käyttö aikuistyypin diabeteksen ilmaantumista, 3) testata hypoteesia kasvikunnasta saatavien yhdisteiden kuten antioksidanttien sekä ravintokuidun yhteydestä aikuistyypin diabeteksen ilmaantuvuuteen, 4) tutkia, minkä osuuden ruokavaliotyypin yhteydestä diabeteksen ilmaantuvuuteen selittävät yksittäiset ruoka-aineet.

8.2 Aineisto ja menetelmät

T u t k i m u s a i n e i s t o

Aineistona käytettiin Kansaneläkelaitoksen autoklinikkatutkimuksen aineistoa, joka kerättiin vuosina 1966–1972. Tutkimus kohdistui maaseutu- ja teollisuuspaikkakuntien ja pienehköjen taajamien väestöihin. Tutkimukseen osallistui 83 % kutsutuista 15 vuotta täyttäneistä miehistä ja naisista 30 eri paikkakunnalta (Aromaa 1981). Vuonna 1967 tutkimukseen liitettiin ravinto-osio, jossa kerättiin 10 054 henkilön ruoankäyttötiedot. Tässä esitettävässä tutkimuksessa aineisto on rajattu 40–69 vuotiaisiin miehiin ja naisiin, joilla ei ollut diabetesta aineiston keruuhetkellä. Aineistosta suljettiin pois ne henkilöt, joiden päivittäinen energian saanti oli alle 800 kcal tai yli 6000 kcal sekä raskaana olevat naiset. Rajausten jälkeen lopullinen tutkimusaineisto käsitti 4304 henkilöä.

Kasviperäisten ravintotekijöiden yhteyttä aikuistyypin diabeteksen myöhempään ilmaantuvuuteen tutkittiin kohorttitutkimusasetelmassa. Tutkimus perustui perustutkimuksessa kerättyihin ruoankäyttötietoihin, joihin on kenttävaiheesta alkaen ja vuoteen 1995 asti liitetty kroonisten tautien ilmaantumistietoja terveyttä koskevista julkisista rekistereistä (Knekt 1988). Tässä tutkimuksessa aikuistyypin diabeteksen ilmaantuvuustiedot 23 vuoden seurannan aikana saatiin Kansaneläkelaitoksen ylläpitämästä Ilmaislääkerekisteristä. Seurannan aikana yhteensä 383 miestä ja naista sairastui aikuistyypin diabetekseen. Tapausten diagnoosit tarkastettiin ja ne noudattavat WHO:n aikuistyypin diabetekselle asettamia diagnostisia kriteerejä (WHO 1985).

Ravintotutkimusmenetelmät

Ruokavaliohaastattelulla selvitettiin tutkimukseen osallistuneiden henkilöiden tavanomainen ruoankäyttö tutkimusta edeltävän vuoden ajalta (Järvinen 1996). Haastattelijat olivat kotitalousalan koulutuksen saaneita henkilöitä. Haastattelu eri ruoka-aineiden kulutuksesta tehtiin etukäteen laaditun luettelon pohjalta, joka sisälsi yli 100 kysymystä Suomessa yleisesti käytetyistä ruoka-aineista. Lisäksi tutkittavilla oli mahdollisuus kertoa myös listaan kuulumattomien ruoka-aineiden kulutuksesta. Käyttökertojen lisäksi tutkittavat arvioivat käyttämiensä ruoka-annosten koon, jonka arvioinnissa käytettiin apuna tilavuusmittoja, ruokamalleja sekä aitoja ruoka-aineita, joiden paino tunnettiin. Myös ruoanvalmistusmenetelmät selvitettiin. Kaikki ruokamäärät muutettiin grammoiksi vuorokautta kohden.

Seuraavassa vaiheessa ruokalajit jaettiin ruoka-aineisiin käyttämällä reseptitiedostoa, joka sisälsi 500 reseptiä. Lopuksi ravintosisältö laskettiin 310 erillisestä ruoka-aineesta käyttämällä ravintosisältötaulukkoa (Rastas et al. 1989). Koska ravintosisältötaulukoissa ei ollut tietoja kaikista tässä tutkimuksessa käytettävistä ravintoaineista, kuitu (Varo et al.1984a; Varo et al.1984b), tokoferolit, tokotrienolit (Piironen 1986), karotenoidit (Heinonen 1990), flavonoidit (Hertog et al. 1993; Hertog 1994; Häkkinen et al. 1999) sekä rasvahapot (Hyvönen et al. 1993; Hyvönen and Koivistoinen 1994) laskettiin käyttäen tietoja, jotka pohjautuivat erikseen analysoituihin ruokiin.

Muut mittausmenetelmät

Tutkimukseen osallistuneista henkilöistä kerättiin monipuolisesti tietoja sairauksien vaaratekijöistä ja terveyden tilasta (Knekt 1988). Tutkittavat täyttivät kyselylomakkeen joka sisälsi kysymyksiä mm. ammatista, raskaudesta, tämän hetkisistä sekä aikaisemmista sairauksista, tupakointitottumuksista ja lääkkeiden käytöstä. Lisäksi tutkittaville tehtiin terveystarkastus, jossa mitattiin pituus, paino ja verenpaine, tehtiin sokerirasituskoe ja otettiin verinäytteet. Kehon painoindeksi laskettiin mitatun pituuden ja painon perusteella. Verinäytteistä määritettiin glukoosi ja seerumin kolesteroli. Kerättyjen verenpainemittaustietojen ja verenpainelääkkeen käytön perusteella muodostettiin neliluokkainen verenpaineluokitus. Glukoosirasituskokeen ja lääkkeiden käyttötietojen perusteella muodostettiin tieto diabeteksesta tutkimushetkellä (Reunanen et al.1983; Reunanen et al. 2000). Pituuden ja painon perusteella laskettiin painoindeksi (Heliövaara and Aromaa 1980). Tupakointi- ja ammattitiedot luokiteltiin yhdeksän luokkaisen pohjoismaisen ammattiluokituksen mukaan (Brockington 1967).

Tilastolliset menetelmät

Eri ruokavaliotyyppien tunnistamiseksi käytettiin faktorianalyysiä (Kim and Mueller 1978). Tutkimushenkilöt järjestettiin kullekin havainnolle laskettujen faktoripisteiden mukaan. Ravinnonsaannin ja sitä määrittävien tekijöiden välisien yhteyksien kuvaamiseen käytettiin lineaarista mallia (Cohen and Cohen 1975). Kohorttitutkimuksessa ruokavaliotyyppien, viljan, kasvisten ja hedelmien sekä niissä olevien ravintoaineiden yhteys aikuistyypin diabeteksen ilmaantuvuuteen analysoitiin Coxin mallilla (Cox 1972). Yhteyksien voimakkuuden mittareina käytettiin mallilla estimoituja suhteellisia riskejä. Potentiaalisia sekoittavia sekä vaikutusta muovaavia tekijöitä (ikä, painoindeksi, energian saanti, tupakointi, maantieteellinen alue sekä diabeteksen sukurasite) hallittiin sijoittamalla niitä malliin. Myös havaittujen yhteyksien trendiä läpi kvartiilien testattiin malliin pohjautuvalla uskottavuusosamäärätestillä siten, että muuttujia käsiteltiin jatkuva-arvoisena kvartiilinumeron mukaan. Sen selvittämiseksi, sisältääkö ruokavaliotyyppiä kuvaava muuttuja mahdollisesti lisäsinformaatiota yli yksittäisten ravintomuuttujien sisällytettiin ruokavaliotyyppiä kuvaava muuttuja samaan malliin yhdessä ruoka-ainemuuttujien kanssa. Tilastollisena ohjelmapakettina käytettiin SAS 6.12, jota käytettiin Kansaneläkelaitoksen ja Kansanterveyslaitoksen yhteistyönä kehittämällä KATI/SAS käyttöliittymällä (KATI 1984).

8.3 Tulokset

Tässä tutkimuksessa tunnistettiin kaksi ruokavaliotyyppiä, jotka nimettiin järkeväksi sekä perinteiseksi ruokavalioksi. Järkeväksi nimetty ruokavaliotyyppi liittyi runsaaseen kasvisten, hedelmien sekä marjojen käyttöön, kun taas perinteiselle tyypille oli ominaisinta voin, perunan, ja täysmaidon käyttö. Järkevä ruokavaliotyyppi ennusti alentunutta diabetesriskiä 23 vuoden seurannassa. Järkevän ruokavalion komponenteista vihreiden kasvisten, hedelmien ja marjojen, öljyn ja margariinin runsaampi käyttö ennusti alentunutta diabeteksen riskiä. Täysjyväviljan käyttö oli käänteisessä yhteydessä aikuistyypin ilmaantuvuuteen, kun seuranta-aika oli rajattu 10 vuoteen. Kuitenkaan yhteyttä ei enää havaittu pitemmässä 23 vuoden seurannassa.

Jatkoanalyyseissä tutkittiin voidaanko ruokavaliotyyppiä kuvaavalla muuttujalla ottaa huomioon mahdollinen ruoka-aineiden välinen synergistinen vaikutus diabeteksen ilmaantuvuuteen. Tätä ruokavaliotyypin mahdollista lisäinformaatiota tutkittiin mallittamalla ruokavaliotyypin komponentteja samaan malliin ruokavaliotyypin kanssa. Analyyseissä havaittiin, että järkevän ruokavaliotyypin ja alentuneen diabetesriskin välinen yhteys selittyi kasvisten, hedelmien ja marjojen sekä öljyn ja margariinien käytöllä.

Tutkimuksessa testattiin kahta kasvikunnan tuotteista saataviin ravintoaineisiin liittyvää hypoteesia. Ravinnon antioksidanttivitamiineista E-vitamiinin sekä karotenoidien saanti oli käänteisessä yhteydessä diabeteksen riskiin. Yksittäisistä tokoferoleista ja tokotrienoleista alfa-tokoferoli, gammatokoferoli, deltatokoferoli sekä betatokotrienoli ennustivat alentunutta diabeteksen riskiä, kun taas karotenoideista betakryptoksantiini oli yhteydessä alentuneeseen diabeteksen riskiin. C-vitamiinin saannilla ei havaittu olevan yhteyttä diabeteksen riskiin. Ravintokuidun, erityisesti viljakuidun runsaampi saanti ennusti alentunutta diabeteksen riskiä.

8.4 Päätelmät

Käänteinen yhteys järkevän ruokavaliotyypin ja diabeteksen riskin välillä selittyi kasvisten, hedelmien, marjojen, sekä öljyn ja margariinin käytöllä, joiden käyttö ennusti myös itsenäisesti alentunutta diabeteksen riskiä. Tulos viittaa siihen, että järkevä ruokavaliotyyppi kuvaa sisältämiensä ruoka-aineiden summaa, eikä se siten näytä sisältävän informaatiota ruoka-aineiden potentiaalisesta synergistisestä vaikutuksesta. Tulokset antavat viitteitä siitä, että aikuistyypin diabeteksen kehittymistä voidaan hillitä käyttämällä kasvikunnasta peräisin olevia ruoka-aineita, erityisesti vihreitä kasviksia, hedelmiä ja marjoja, ruokaöljyä sekä margariinia. Tämä tutkimus vahvistaa hypoteesia viljakuidun sekä antioksidanttivitamiinien diabetesta ehkäisevästä vaikutuksesta. Kuitenkin lisää tutkimuksia tarvitaan sen selvittämiseksi johtuuko kasvikunnasta peräisin olevan ruoan käänteinen yhteys diabeteksen riskiin hypoteesin mukaisten ravintoaineiden, muiden kasvikunnasta saatavien ravintoaineiden tai muiden komponenttien saannista vai kasvikunnan tuotteiden käyttöön liittyvistä muista elintapatekijöistä.

9 ACKNOWLEDGMENTS

This work was carried out in the Department of Health and Functional Capacity, National Public Institute in 2000 – 2005. The data used in this work is based on the Finnish Mobile Clinic Health Examination Survey carried out by the Social Insurance Institution of Finland. Besides these institutions a band of colleagues have contributed to the completion of this thesis. I owe my sincere thanks to these people for their contribution. The financial support from the Doctoral Programs in Public Health and the Social Insurance Institution that have made this thesis possible are gratefully acknowledged.

I also express my deepest gratitude to:

Research Professor Paul Knekt, my principal supervisor, for his firm belief in me and teaching me nearly everything that I know about nutritional epidemiology. His pedagogical skills and his expertise in the field of epidemiology are gratefully acknowledged.

My supervisors, Docent Ritva Järvinen and Research Professor Antti Reunanen, for their continuous support and guidance. I greatly appreciate Ritva's rapid and never failing responses to my queries and Antti's superior knowledge on diabetes issues. I feel sincerely privileged to be supervised by three world-class specialists.

Professor Leena Räsänen and Docent Leena Moilanen, the official reviewers of this thesis, for constructive criticism and suggestions for improving this thesis.

Research Professor Arpo Aromaa, Head of the Department of Health and Functional Capacity, for the opportunity to be a member of the staff of the Department and for administrative, technical and material support.

Docent Markku Heliövaara and Tommi Härkänen PhD, my coauthors, for their collaboration and valuable advice during this process.

Harri Rissanen, Esa Virtala, Sirkka Rinne, Pirkko Alha and Virpi Killström for taking care of day-to-day business and assisting in many practical issues in computing and data management. You are the ones who keep the engine running!

The personnel of the library at National Public Health Institute for providing the relevant literature and the English Centre Oy for revising the English language of this thesis.

All the 'Lions, Tigers and Pumas' working at TTO, for sharing my coffee table, for their friendship and keeping my spirits up during these arduous years. Anna

Kattainen PhD, as a former room-mate is acknowledged for sharing the office and giving me support on those days when the sun did not shine.

Last, but not least I owe my sincere gratitude to my dear family and friends for their endless support and especially my beloved Tiina, for those long walks round the pond 'Valkeinen' and for sharing the bright and dark moments of life with me. "Tuus Totus".

Helsinki 2005 *Jukka Montonen*

REFERENCES

Abahusain MA, Wright J, Dickerson JW and de Vol EB. Retinol, alpha-tocopherol and carotenoids in diabetes. Eur J Clin Nutr 1999;53:630-635.

Adlercreutz H and Mazur W. Phyto-oestrogens and Western diseases. Ann Med 1997;29:95-120.

Akiyama T, Ishida J, Nakagawa S, Ogawara H, Watanabe S, Itoh N, Shibuya M and Fukami Y. Genistein, a specific inhibitor of tyrosine-specific protein kinases. J Biol Chem 1987;262:5592-5595.

Alberti KG and Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1:diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539-553.

Alberti G, Zimmet P, Shaw J, Bloomgarden Z, Kaufman F and Silink M. Type 2 diabetes in the young: the evolving epidemic: the international diabetes federation consensus workshop. Diabetes Care 2004;27:1798-1811.

Althuis MD, Jordan NE, Ludington EA and Wittes JT. Glucose and insulin responses to dietary chromium supplements:a meta-analysis. Am J Clin Nutr 2002;76:148-155.

Amos AF, McCarty DJ and Zimmet P. The rising global burden of diabetes and its complications:estimates and projections to the year 2010. Diabet Med 1997;14 Suppl 5:S1-85.

Anderson JW, Midgley WR and Wedman B. Fiber and diabetes. Diabetes Care 1979;2:369-377.

Anderson RA. Chromium in the prevention and control of diabetes. Diabetes Metab 2000;26:22-27.

Aromaa A Kohonnut verenpaine ja sen kansanterveydellinen merkitys Suomessa.(Epidemiology and public health impact of high blood pressure in Finland.) (In Finnish with an English summary.). Publications of the Social Insurance institution, AL:17.Helsinki, 1981.

Ashby JP, Deacon AC and Frier BM. Glycosylated haemoglobin. Part I:Measurement and clinical interpretation. Diabet Med 1985;2:83-85.

Audelin MC and Genest J, Jr. Homocysteine and cardiovascular disease in diabetes mellitus. Atherosclerosis 2001;159:497-511.

Barker DJ, Hales CN, Fall CH, Osmond C, Phipps K and Clark PM. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X):relation to reduced fetal growth. Diabetologia 1993;36:62-67.

Bhathena SJ and Velasquez MT. Beneficial role of dietary phytoestrogens in obesity and diabetes. Am J Clin Nutr 2002;76:1191-1201.

Bjorck I, Granfeldt Y, Liljeberg H, Tovar J and Asp NG. Food properties affecting the digestion and absorption of carbohydrates. Am J Clin Nutr 1994;59:699S-705S.

Block G, Norkus E, Hudes M, Mandel S and Helzlsouer K. Which plasma antioxidants are most related to fruit and vegetable consumption? Am J Epidemiol 2001;154:1113-1118.

Boeing H, Weisgerber UM, Jeckel A, Rose HJ and Kroke A. Association between glycated hemoglobin and diet and other lifestyle factors in a nondiabetic population:cross-sectional evaluation of data from the Potsdam cohort of the European Prospective Investigation into Cancer and Nutrition Study. Am J Clin Nutr 2000;71:1115-1122.

Boushey CJ, Beresford SA, Omenn GS and Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. JAMA 1995;274:1049-1057.

Brockington F World health. Appendix VIII. The International Standard Classification of Occupations. Churchill. London, 1967

Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001;414:813-820.

Brugård Konde Å, Staffas A, Dahl P and Becker W. Carotenoids in Foodstuff in Sweden (In Swedish with an English summary). National Food Administration. Uppsala, 1996.

Brunzell JD, Robertson RP, Lerner RL, Hazzard WR, Ensinck JW, Bierman EL and Porte D, Jr. Relationships between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance tests. J Clin Endocrinol Metab 1976;42:222-229.

Burstein R, Epstein Y, Shapiro Y, Charuzi I and Karnieli E. Effect of an acute bout of exercise on glucose disposal in human obesity. J Appl Physiol 1990;69:299-304.

Ceriello A, Giugliano D, Quatraro A, Donzella C, Dipalo G and Lefebvre PJ. Vitamin E reduction of protein glycosylation in diabetes. New prospect for prevention of diabetic complications? Diabetes Care 1991;14:68-72.

Ceriello A. Oxidative stress and glycemic regulation. Metabolism 2000;49:S27-S29.

Chico A, Perez A, Cordoba A, Arcelus R, Carreras G, de Leiva A, Gonzalez-Sastre F and Blanco-Vaca F. Plasma homocysteine is related to albumin excretion rate in patients with diabetes mellitus:a new link between diabetic nephropathy and cardiovascular disease? Diabetologia 1998;41:684-693.

Cohen J and Cohen P. Applied multiple regression/correlation analysis for behavioral sciences. Wiley. New York, 1975.

Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC and Speizer FE. Diet and risk of clinical diabetes in women. Am J Clin Nutr 1992;55:1018-1023.

Colwell JA. Elevated plasma homocysteine and diabetic vascular disease. Diabetes Care 1997;20:1805-1806.

Cox D. Regression models and life-tables. J R Stat Soc B 1972;34:187-220.

Cronin CC, McPartlin JM, Barry DG, Ferriss JB, Scott JM and Weir DG. Plasma homocysteine concentrations in patients with type 1 diabetes. Diabetes Care 1998;21:1843-1847.

de Valk HW, Verkaaik R, van Rijn HJ, Geerdink RA and Struyvenberg A. Oral magnesium supplementation in insulin-requiring Type 2 diabetic patients. Diabet Med 1998;15:503-507.

Duncan GE, Perri MG, Theriaque DW, Hutson AD, Eckel RH and Stacpoole PW. Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults. Diabetes Care 2003;26:557-562.

Edwards AJ, Nguyen CH, You CS, Swanson JE, Emenhiser C and Parker RS. Alpha- and beta-carotene from a commercial puree are more bioavailable to humans than from boiled-mashed carrots, as determined using an extrinsic stable isotope reference method. J Nutr 2002;132:159-167.

Ekblond A, Mellemkjaer L, Tjonneland A, Suntum M, Stripp C, Overvad K, Johansen C and Olsen JH. A cross-sectional study of dietary habits and urinary glucose excretion - a predictor of non-insulin-dependent diabetes mellitus. Eur J Clin Nutr 2000;54:434-439.

Eriksson J, Taimela S and Koivisto VA. Exercise and the metabolic syndrome. Diabetologia 1997;40:125-135.

Esmaillzadeh A, Mirmiran P and Azizi F. Whole-grain consumption and the metabolic syndrome:a favorable association in Tehranian adults. Eur J Clin Nutr 2005;59:353-62.

Facchini F, Coulston AM and Reaven GM. Relation between dietary vitamin intake and resistance to insulin-mediated glucose disposal in healthy volunteers. Am J Clin Nutr 1996;63:946-949.

Facchini FS, Humphreys MH, DoNascimento CA, Abbasi F and Reaven GM. Relation between insulin resistance and plasma concentrations of lipid hydroperoxides, carotenoids, and tocopherols. Am J Clin Nutr 2000;72:776-779.

Ferrannini E, Natali A, Bell P, Cavallo-Perin P, Lalic N and Mingrone G. Insulin resistance and hypersecretion in obesity. European Group for the Study of Insulin Resistance (EGIR). J Clin Invest1997;100:1166-1173.

Feskens EJ and Kromhout D. Habitual dietary intake and glucose tolerance in euglycaemic men:the Zutphen Study. Int J Epidemiol1990;19:953-959.

Feskens EJ, Bowles CH and Kromhout D. Carbohydrate intake and body mass index in relation to the risk of glucose intolerance in an elderly population. Am J Clin Nutr 1991;54:136-140.

Feskens EJ, Loeber JG and Kromhout D. Diet and physical activity as determinants of hyperinsulinemia:the Zutphen Elderly Study. Am J Epidemiol 1994;140:350-360.

Feskens EJ, Virtanen SM, Räsänen L, Tuomilehto J, Stengård J, Pekkanen J, Nissinen A and Kromhout D. Dietary factors determining diabetes and impaired glucose tolerance. A 20-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study. Diabetes Care 1995;18:1104-1112.

Folsom AR, Kushi LH and Hong CP. Physical activity and incident diabetes mellitus in postmenopausal women. Am J Public Health 2000;90:134-138.

Ford ES and Mokdad AH. Fruit and vegetable consumption and diabetes mellitus incidence among U.S. adults. Prev Med 2001;32:33-39.

Ford ES, Will JC, Bowman BA and Narayan KM. Diabetes mellitus and serum carotenoids:findings from the Third National Health and Nutrition Examination Survey. Am J Epidemiol 1999;149:168-176.

Forsén T, Eriksson J, Tuomilehto J, Reunanen A, Osmond C and Barker D. The fetal and childhood growth of persons who develop type 2 diabetes. Ann Intern Med 2000;133:176-182.

Foster-Powell K, Holt SH and Brand-Miller JC. International table of glycemic index and glycemic load values:2002. Am J Clin Nutr 2002;76:5-56.

Franz MJ, Bantle JP, Beebe CA, Brunzell JD, Chiasson JL, Garg A, Holzmeister LA, Hoogwerf B, Mayer-Davis E, Mooradian AD, Purnell JQ and Wheeler M. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. Diabetes Care 2002;25:148-198.

Fraser GE. Associations between diet and cancer, ischemic heart disease, and all-cause mortality in non-Hispanic white California Seventh-day Adventists. Am J Clin Nutr 1999;70:532S-538S.

Frei B, England L and Ames BN. Ascorbate is an outstanding antioxidant in human blood plasma. Proc Natl Acad Sci U S A 1989;86:6377-6381.

Fukagawa NK, Anderson JW, Hageman G, Young VR and Minaker KL. High-carbohydrate, high-fiber diets increase peripheral insulin sensitivity in healthy young and old adults. Am J Clin Nutr 1990;52:524-528.

Fung TT, Rimm EB, Spiegelman D, Rifai N, Tofler GH, Willett WC and Hu FB. Association between dietary patterns and plasma biomarkers of obesity and cardiovascular disease risk. Am J Clin Nutr 2001a;73:61-67.

Fung TT, Willett WC, Stampfer MJ, Manson JE and Hu FB. Dietary patterns and the risk of coronary heart disease in women. Arch Intern Med 2001b;161:1857-1862.

Fung TT, Hu FB, Pereira MA, Liu S, Stampfer MJ, Colditz GA and Willett WC. Whole-grain intake and the risk of type 2 diabetes:a prospective study in men. Am J Clin Nutr 2002;76:535-540.

Fung TT, Schulze M, Manson JE, Willett WC and Hu FB. Dietary patterns, meat intake, and the risk of type 2 diabetes in women. Arch Intern Med 2004;164:2235-2240.

Gelding SV, Coldham N, Niththyananthan R, Anyaoku V and Johnston DG. Insulin resistance with respect to lipolysis in non-diabetic relatives of European patients with type 2 diabetes. Diabet Med 1995;12:66-73.

Gittelsohn J, Wolever TM, Harris SB, Harris-Giraldo R, Hanley AJ and Zinman B. Specific patterns of food consumption and preparation are associated with diabetes and obesity in a Native Canadian community. J Nutr 1998;128:541-547.

Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan D, Peterson CM and Sacks DB. Tests of glycemia in diabetes. Diabetes Care 2004;27:1761-1773.

Goodman-Gruen D and Kritz-Silverstein D. Usual dietary isoflavone intake is associated with cardiovascular disease risk factors in postmenopausal women. J Nutr 2001;131:1202-1206.

Gordon M. Dietary antioxidants in disease prevention. Nat Prod Rep 1996;13:265-273.

Granfeldt Y, Hagander B and Bjorck I. Metabolic responses to starch in oat and wheat products. On the importance of food structure, incomplete gelatinization or presence of viscous dietary fibre. Eur J Clin Nutr 1995;49:189-199.

Grundy SM, Brewer HB, Jr., Cleeman JI, Smith SC, Jr. and Lenfant C. Definition of metabolic syndrome:Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433-438.

Gums JG. Magnesium in cardiovascular and other disorders. Am J Health Syst Pharm 2004;61:1569-1576.

Haber GB, Heaton KW, Murphy D and Burroughs LF. Depletion and disruption of dietary fibre. Effects on satiety, plasma-glucose, and serum-insulin. Lancet 1977;2:679-682.

Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C and Winter PD. Fetal and infant growth and impaired glucose tolerance at age 64. BMJ 1991;303:1019-1022.

Halliwell B and Gutteridge J. Free radicals in biology and medicine. Oxford University Press. New York, 1989.

Hayden MR and Tyagi SC. Homocysteine and reactive oxygen species in metabolic syndrome, type 2 diabetes mellitus, and atheroscleropathy:The pleiotropic effects of folate supplementation. Nutr J 2004;3:4.

Heinonen M Carotenoids and retinoids in Finnish foods and the average diet. Department of Food Chemistry and Technology, University of Helsinki, EKT:811. Helsinki, 1990.

Helderman JH, Elahi D, Andersen DK, Raizes GS, Tobin JD, Shocken D and Andres R. Prevention of the glucose intolerance of thiazide diuretics by maintenance of body potassium. Diabetes 1983;32:106-111.

Heliövaara M and Aromaa A Suomalaisten aikuisten pituus, paino ja lihavuus. (Height, weight and obesity of Finnish adults.)(In Finnish with an English summary.) Publications of the Social Insurance Institution, ML:19.Helsinki, 1980

Helmrich SP, Ragland DR, Leung RW and Paffenbarger RS, Jr. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. N Engl J Med 1991;325:147-152.

Hermansen K, Sondergaard M, Hoie L, Carstensen M and Brock B. Beneficial effects of a soy-based dietary supplement on lipid levels and cardiovascular risk markers in type 2 diabetic subjects. Diabetes Care 2001;24:228-233.

Hertog M Flavonols and flavones in foods ant their relation with cancer and coronary heart disease risk. Koninklijke Bibliotheek, DIP-data. Hague, 1994.

Hertog MG, Hollman PC, Katan MB and Kromhout D. Intake of potentially anticarcinogenic flavonoids and their determinants in adults in The Netherlands. Nutr Cancer 1993;20:21-29.

Hodge AM, Dowse GK and Zimmet PZ. Diet does not predict incidence or prevalence of non-insulin-dependent diabetes in Nauruans. Asia Pacific J Clin Nutr 1993;2:35-41.

Hodge AM, Montgomery J, Dowse GK, Mavo B, Watt T and Zimmet PZ. A case-control study of diet in newly diagnosed NIDDM in the Wanigela people of Papua New Guinea. Diabetes Care 1996;19:457-462.

Hoffman WS. A rapid photoelectric method for the determination of glucose in blood and urine. J Biol Chem 1937;120:50-555.

Hofmann MA, Kohl B, Zumbach MS, Borcea V, Bierhaus A, Henkels M, Amiral J, Schmidt AM, Fiehn W, Ziegler R, Wahl P and Nawroth PP. Hyperhomocyst(e)inemia and endothelial dysfunction in IDDM. Diabetes Care 1998;21:841-848.

Hu FB. Dietary pattern analysis:a new direction in nutritional epidemiology. Curr Opin Lipidol 2002;13:3-9.

Hu FB, Sigal RJ, Rich-Edwards JW, Colditz GA, Solomon CG, Willett WC, Speizer FE and Manson JE. Walking compared with vigorous physical activity and risk of type 2 diabetes in women:a prospective study. JAMA 1999a;282:1433-1439.

Hu FB, Rimm E, Smith-Warner SA, Feskanich D, Stampfer MJ, Ascherio A, Sampson L and Willett WC. Reproducibility and validity of dietary patterns assessed with a food- frequency questionnaire. Am J Clin Nutr 1999b;69:243-249.

Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WC and Rimm EB. Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. Arch Intern Med 2001a;161:1542-1548.

Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG and Willett WC. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 2001b;345:790-797.

Hu FB, van Dam RM and Liu S. Diet and risk of Type II diabetes:the role of types of fat and carbohydrate. Diabetologia 2001c;44:805-817.

Huang TC, Chen CP, Wefler V and Raftery A. A stable reagent for the Lieberman-Burchard reaction. Application to rapid serum cholesterol determination. Anal Chem 1961;33:1405-1507.

Hue L. Gluconeogenesis and its regulation. Diabetes Metab Rev 1987;3:111-126.

Hyvönen L and Koivistoinen P. Fatty acid analysis, TAG equivalents as net fat value, and nutritional attributes of fish fish products. J Food Compost Anal 1994;7:44-58.

Hyvönen L, Lampi A-M, Varo P and Koivistoinen P. Fatty acid analysis, TAG equivalents as net fat values, and nutritional attributes of commercial fats and oils. J Food Compost Anal 1993;6:24-40.

Häkkinen S, Kärenlampi SO, Heinonen M, Mykkänen HM and Törrönen AR. Content of flavonoids quercetin, myricetin, and kaempferol in 25 edible berries. J Agric Food Chem 1999;47:2274-2279.

Iritani N, Sugimoto T, Fukuda H, Komiya M and Ikeda H. Dietary soybean protein increases insulin receptor gene expression in Wistar fatty rats when dietary polyunsaturated fatty acid level is low. J Nutr 1997;127:1077-1083.

Jacobs DR, Jr. and Murtaugh MA. It's more than an apple a day:an appropriately processed, plant-centered dietary pattern may be good for your health. Am J Clin Nutr 2000;72:899-900.

Jacobs DR, Jr. and Steffen LM. Nutrients, foods, and dietary patterns as exposures in research:a framework for food synergy. Am J Clin Nutr 2003;78:S508-S513.

Jacobson HN and Stanton JL. Pattern analysis in nutrition. Clin Nutr 1986;5:249-253.

Jarrett RJ. Epidemiology and public health aspects of non-insulin-dependent diabetes mellitus. Epidemiol Rev 1989;11:151-171.

Jayagopal V, Albertazzi P, Kilpatrick ES, Howarth EM, Jennings PE, Hepburn DA and Atkin SL. Beneficial effects of soy phytoestrogen intake in postmenopausal women with type 2 diabetes. Diabetes Care 2002;25:1709-1714.

Jenkins DJ, Leeds AR, Gassull MA, Cochet B and Alberti GM. Decrease in postprandial insulin and glucose concentrations by guar and pectin. Ann Intern Med 1977;86:20-23.

Jenkins DJ, Wolever TM, Buckley G, Lam KY, Giudici S, Kalmusky J, Jenkins AL, Patten RL, Bird J and Wong GS. Low-glycemic-index starchy foods in the diabetic diet. Am J Clin Nutr 1988;48:248-254.

Jenkins DJ, Kendall CW, Augustin LS, Franceschi S, Hamidi M, Marchie A, Jenkins AL and Axelsen M. Glycemic index:overview of implications in health and disease. Am J Clin Nutr 2002;76:S266-S273.

Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC and Hu FB. Nut and peanut butter consumption and risk of type 2 diabetes in women. JAMA 2002;288:2554-2560.

John JH, Ziebland S, Yudkin P, Roe LS and Neil HA. Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure:a randomised controlled trial. Lancet 2002;359:1969-1974.

Juntunen KS, Niskanen LK, Liukkonen KH, Poutanen KS, Holst JJ and Mykkänen HM. Postprandial glucose, insulin, and incretin responses to grain products in healthy subjects. Am J Clin Nutr 2002;75:254-262.

Juntunen KS, Laaksonen DE, Autio K, Niskanen LK, Holst JJ, Savolainen KE, Liukkonen KH, Poutanen KS and Mykkänen HM. Structural differences between rye and wheat breads but not total fiber content may explain the lower postprandial insulin response to rye bread. Am J Clin Nutr 2003a;78:957-964.

Juntunen KS, Laaksonen DE, Poutanen KS, Niskanen LK and Mykkänen HM. High-fiber rye bread and insulin secretion and sensitivity in healthy postmenopausal women. Am J Clin Nutr 2003b;77:385-391.

Järvinen R, Seppänen R and Knekt P. Short-term and long-term reproducibility of dietary history interview data. Int J Epidemiol1993a;22:520-527.

Järvinen R, Knekt P, Seppänen R, Heinonen M and Aaran RK. Dietary determinants of serum beta-carotene and serum retinol. Eur J Clin Nutr 1993b;47:31-41.

Järvinen R, Knekt P, Seppänen R, Reunanen A, Heliövaara M, Maatela J and Aromaa A. Antioxidant vitamins in the diet:relationships with other personal characteristics in Finland. J Epidemiol Community Health 1994;48:549-554.

Järvinen R. Epidemiological Follow-up Study on Dietary Antioxidant Vitamins. Results from the Finnish Mobile Clinic Health Examination Survey. The Social Insurance Institution, Studies in social security and health:11. Helsinki, 1996

Kahn BB. Type 2 diabetes:when insulin secretion fails to compensate for insulin resistance. Cell 1998;92:593-596.

Kaji H, Kurasaki M, Ito K, Saito T, Saito K, Niioka T, Kojima Y, Ohsaki Y, Ide H and Tsuji M. Increased lipoperoxide value and glutathione peroxidase activity in blood plasma of type 2 (non-insulin-dependent) diabetic women. Klin Wochenschr.1985;63:765-768.

Kangas T Diabeetikkojen terveyspalvelut ja niiden kustannukset. Helsinkiläisten diabeetikkojen verrokkikontrolloitu poikkileikkaustutkimus (The consumption and direct costs of health care services among persons with diabetes in Helsinki. A case controlled cross-sectional study of the fiscal year 1997. In Finnish with an English summary). Social insurance Institution. Studies in social security and health: 67.Helsinki, 2002

Kao WH, Folsom AR, Nieto FJ, Mo JP, Watson RL and Brancati FL. Serum and dietary magnesium and the risk for type 2 diabetes mellitus:the Atherosclerosis Risk in Communities Study. Arch Intern Med 1999;159:2151-2159.

KATI Kansaneläkelaitoksen tilastollinen ohjelmisto. (Käsikirja). Kansaneläkelaitos. Helsinki, 1984.

Kay RM and Strasberg SM. Origin, chemistry, physiological effects and clinical importance of dietary fibre. Clin Invest Med 1978;1:9-24.

Kiehm TG, Anderson JW and Ward K. Beneficial effects of a high carbohydrate, high fiber diet on hyperglycemic diabetic men. Am J Clin Nutr 1976;29:895-899.

Kim J-O and Mueller C Factor analysis statistical methods and practical issues. Sage Publications. Beverly Hills Ca, 1978

King H, Aubert RE and Herman WH. Global burden of diabetes, 1995-2025:prevalence, numerical estimates, and projections. Diabetes Care 1998;21:1414-1431

Klaukka T, Martikainen, J., Kalimo, E. Drug utilization in Finland 1967-1987. Social Incurance Institution. Helsinki, 1990.

Klöppel G, Lohr M, Habich K, Oberholzer M and Heitz PU. Islet pathology and the pathogenesis of type 1 and type 2 diabetes mellitus revisited. Surv Synth Pathol Res 1985;4:110-125

Knekt P. Serum alpha-tocopherol and the risk of cancer. Publications of the Social Insurance Institution, ML:83. Helsinki, 1988.

Knekt P, Seppänen R and Aaran RK. Determinants of serum alpha-tocopherol in Finnish adults. Preventive Medicine.1988;17:725-735.

Knekt P, Reunanen A, Marniemi J, Leino A and Aromaa A. Low vitamin E status is a potential risk factor for insulin-dependent diabetes mellitus. J Intern Med 1999;245:99-102.

Knekt P, Kumpulainen J, Järvinen R, Rissanen H, Heliövaara M, Reunanen A, Hakulinen T and Aromaa A. Flavonoid intake and risk of chronic diseases. Am J Clin Nutr 2002;76:560-568.

Knowler WC, Pettitt DJ, Savage PJ and Bennett PH. Diabetes incidence in Pima indians:contributions of obesity and parental diabetes. Am J Epidemiol 1981;113:144-156.

Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA and Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.

Koskinen EH. Suomalaisten ruoankäyttö ja ravinnonsaanti vuosina 1967-1969 autoklinikan ravintotutkimusten valossa. (The food consumption and nutrient intake of Finns in 1967 to 1969.) (In Finnish with an English summary.) Publications of the Socian Insurance Institution, ML:6. Helsinki, 1975.

Krinsky NI. Mechanism of action of biological antioxidants. Proc Soc Exp Biol Med 1992;200:248-254.

Kuzuya T, Nakagawa S, Satoh J, Kanazawa Y, Iwamoto Y, Kobayashi M, Nanjo K, Sasaki A, Seino Y, Ito C, Shima K, Nonaka K and Kadowaki T. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. Diabetes Res Clin Pract 2002;55:65-85.

Kähler W, Kuklinski B, Ruhlmann C and Plotz C. Diabetes mellitus--a free radical-associated disease. Results of adjuvant antioxidant supplementation. Z Gesamte Inn Med 1993;48:223-232.

Laakso M. How good a marker is insulin level for insulin resistance? Am J Epidemiol 1993;137:959-965.

Laaksonen DE, Lakka TA, Lakka HM, Nyyssonen K, Rissanen T, Niskanen LK and Salonen JT. Serum fatty acid composition predicts development of impaired fasting glycaemia and diabetes in middle-aged men. Diabet Med 2002;19:456-464.

Lavigne C, Marette A and Jacques H. Cod and soy proteins compared with casein improve glucose tolerance and insulin sensitivity in rats. Am J Physiol Endocrinol Metab 2000;278:491-500.

Lebovitz HE. Diagnosis, classification, and pathogenesis of diabetes mellitus. J Clin Psychiatry 2001;62 Suppl 27:5-9.

Leinonen JS, Alho H, Harmoinen A, Lehtimaki T and Knip M. Unaltered antioxidant activity of plasma in subjects at increased risk for IDDM. Free Radic Res 1998;29:159-164.

Leinonen K, Liukkonen K, Poutanen K, Uusitupa M and Mykkänen H. Rye bread decreases postprandial insulin response but does not alter glucose response in healthy Finnish subjects. Eur J Clin Nutr 1999;53:262-267.

Liese AD, Roach AK, Sparks KC, Marquart L, D'Agostino RB, Jr. and Mayer-Davis EJ. Whole-grain intake and insulin sensitivity:the Insulin Resistance Atherosclerosis Study. Am J Clin Nutr 2003;78:965-971.

Linassier C, Pierre M, Le Pecq JB and Pierre J. Mechanisms of action in NIH-3T3 cells of genistein, an inhibitor of EGF receptor tyrosine kinase activity. Biochem Pharmacol 1990;39:187-193.

Liu S. Whole-grain foods, dietary fiber, and type 2 diabetes:searching for a kernel of truth. Am J Clin Nutr 2003a;77:527-529.

Liu RH. Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals. Am J Clin Nutr 2003b;78:S517- S520.

Liu S, Ajani U, Chae C, Hennekens C, Buring JE and Manson JE. Long-term beta-carotene supplementation and risk of type 2 diabetes mellitus:a randomized controlled trial. JAMA 1999;282:1073-1075.

Liu S, Manson JE, Stampfer MJ, Hu FB, Giovannucci E, Colditz GA, Hennekens CH and Willett WC. A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. Am J Public Health 2000;90:1409-1415.

Lopez-Ridaura R, Willett WC, Rimm EB, Liu S, Stampfer MJ, Manson JE and Hu FB. Magnesium intake and risk of type 2 diabetes in men and women. Diabetes Care 2004;27:134-140.

Lovejoy J and DiGirolamo M. Habitual dietary intake and insulin sensitivity in lean and obese adults. Am J Clin Nutr 1992;55:1174-1179.

Lundgren H, Bengtsson C, Blohme G, Isaksson B, Lapidus L, Lenner RA, Saaek A and Winther E. Dietary habits and incidence of noninsulin-dependent diabetes mellitus in a population study of women in Gothenburg, Sweden. Am J Clin Nutr 1989;49:708-712.

Lynch J, Helmrich SP, Lakka TA, Kaplan GA, Cohen RD, Salonen R and Salonen JT. Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. Arch Intern Med 1996;156:1307-1314.

Maddux BA, See W, Lawrence JC, Jr., Goldfine AL, Goldfine ID and Evans JL. Protection against oxidative stress-induced insulin resistance in rat L6 muscle cells by mircomolar concentrations of alpha-lipoic acid. Diabetes 2001;50:404-410.

Manolio TA, Savage PJ, Burke GL, Hilner JE, Liu K, Orchard TJ, Sidney S and Oberman A. Correlates of fasting insulin levels in young adults:the CARDIA study. J Clin Epidemiol 1991;44:571-578.

Manson JE, Rimm EB, Stampfer MJ, Colditz GA, Willett WC, Krolewski AS, Rosner B, Hennekens CH and Speizer FE. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. Lancet 1991;338:774-778.

Manson JE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC and Hennekens CH. A prospective study of exercise and incidence of diabetes among US male physicians. JAMA 1992;268:63-67.

Markovits J, Linassier C, Fosse P, Couprie J, Pierre J, Jacquemin-Sablon A, Saucier JM, Le Pecq JB and Larsen AK. Inhibitory effects of the tyrosine kinase inhibitor genistein on mammalian DNA topoisomerase II. Cancer Res 1989;49:5111-5117.

Marlett JA, McBurney MI and Slavin JL. Position of the American Dietetic Association:health implications of dietary fiber. J Am Diet Assoc 2002;102:993-1000.

Maron DJ, Fair JM and Haskell WL. Saturated fat intake and insulin resistance in men with coronary artery disease. The Stanford Coronary Risk Intervention Project Investigators and Staff. Circulation 1991;84:2020-2027.

Marshall JA, Hamman RF and Baxter J. High-fat, low-carbohydrate diet and the etiology of non-insulin-dependent diabetes mellitus:the San Luis Valley Diabetes Study. Am J Epidemiol 1991;134:590-603.

Marshall JA, Hoag S, Shetterly S and Hamman RF. Dietary fat predicts conversion from impaired glucose tolerance to NIDDM. The San Luis Valley Diabetes Study. Diabetes Care 1994;17:50-56.

Marshall JA, Bessesen DH and Hamman RF. High saturated fat and low starch and fibre are associated with hyperinsulinaemia in a non-diabetic population:the San Luis Valley Diabetes Study. Diabetologia 1997;40:430-438.

Mayer EJ, Newman B, Quesenberry CP, Jr. and Selby JV. Usual dietary fat intake and insulin concentrations in healthy women twins. Diabetes Care 1993;16:1459-1469.

Mayer-Davis EJ, Monaco JH, Hoen HM, Carmichael S, Vitolins MZ, Rewers MJ, Haffner SM, Ayad MF, Bergman RN and Karter AJ. Dietary fat and insulin sensitivity in a triethnic population:the role of obesity. The Insulin Resistance Atherosclerosis Study (IRAS). Am J Clin Nutr 1997;65:79-87.

Mayer-Davis EJ, Costacou T, King I, Zaccaro DJ and Bell RA. Plasma and dietary vitamin E in relation to incidence of type 2 diabetes:The Insulin Resistance and Atherosclerosis Study (IRAS). Diabetes Care 2002;25:2172-2177.

McKeown NM, Meigs JB, Liu S, Wilson PW and Jacques PF. Whole-grain intake is favorably associated with metabolic risk factors for type 2 diabetes and cardiovascular disease in the Framingham Offspring Study. Am J Clin Nutr 2002;76:390-398.

McKeown NM, Meigs JB, Liu S, Saltzman E, Wilson PW and Jacques PF. Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort. Diabetes Care 2004;27:538-546.

McLaughlin PJ and Weihrauch JL. Vitamin E content of foods. J Am Diet Assoc 1979;75:647-665.

McPhillips JB, Barrett-Connor E and Wingard DL. Cardiovascular disease risk factors prior to the diagnosis of impaired glucose tolerance and non-insulin-dependent diabetes mellitus in a community of older adults. Am J Epidemiol 1990;131:443-453.

Mensink M, Feskens EJ, Saris WH, De Bruin TW and Blaak EE. Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht (SLIM):preliminary results after one year. Int J Obes Relat Metab Disord 2003;27:377-384.

Metzger BE, Cho NH, Roston SM and Radvany R. Prepregnancy weight and antepartum insulin secretion predict glucose tolerance five years after gestational diabetes mellitus. Diabetes Care 1993;16:1598-1605.

Meyer KA, Kushi LH, Jacobs DR, Jr., Slavin J, Sellers TA and Folsom AR. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. Am J Clin Nutr 2000;71:921-930.

Meyer KA, Kushi LH, Jacobs DR, Jr. and Folsom AR. Dietary fat and incidence of type 2 diabetes in older Iowa women. Diabetes Care 2001;24:1528-1535.

Mikhailidis DP, Papadakis JA and Ganotakis ES. Smoking, diabetes and hyperlipidaemia. J R Soc Health 1998;118:91-93.

Ministry of Agriculture and Forestry. Ravintotase 2001 ja 2002 (ennakko). Ministry of Agriculture and Forestry. Helsinki, 2003.

Modan M, Halkin H, Fuchs Z, Lusky A, Chetrit A, Segal P, Eshkol A, Almog S and Shefi M. Hyperinsulinemia--a link between glucose intolerance, obesity, hypertension, dyslipoproteinemia, elevated serum uric acid and internal cation imbalance. Diabete Metab 1987;13:375-380.

Montonen J, Knekt P, Jarvinen R and Reunanen A. Dietary antioxidant intake and risk of type 2 diabetes:response to Granado-lorencio and Olmedilla-alonso. Diabetes Care 2004;27:1845-1846.

Mooy JM, Grootenhuis PA, de Vries H, Valkenburg HA, Bouter LM, Kostense PJ and Heine RJ. Prevalence and determinants of glucose intolerance in a Dutch caucasian population. The Hoorn Study. Diabetes Care 1995;18:1270-1273.

Murthy VK, Shipp JC, Hanson C and Shipp DM. Delayed onset and decreased incidence of diabetes in BB rats fed free radical scavengers. Diabetes Res Clin Pract 1992;18:11-16.

Narayan KM, Boyle JP, Thompson TJ, Sorensen SW and Williamson DF. Lifetime risk for diabetes mellitus in the United States. JAMA 2003;290:1884-1890.

National Nutrition Council. Finnish Nutrition Recommendations. Committee report 1998:7. Ministry of Agriculture and Forestry. Helsinki, 1999.

Nielsen FH. Chromium. In book:Shils M, Olson J, Shike M, Eds. Modern Nutrition in Health and Disease. Lea & Febiger. Philadelphia,1994.

Niemi M and Winell K. Diabetes Suomessa Väliraportti tutkimusprojektissa Alueellinen vertailu hoidon laadun mittariksi. STAKES-tilastot, National Research and Development Centre for Welfare and Health. Helsinki, 2005 (Accessed March 1, 2005). Available at: http://www.stakes.info/files/pdf/raportit/diabetesraportti.pdf

Nurjhan N, Consoli A and Gerich J. Increased lipolysis and its consequences on gluconeogenesis in non-insulin-dependent diabetes mellitus. J Clin Invest1992;89:169-175.

Oberley LW. Free radicals and diabetes. Free Radic Biol Med 1988;5:113-124.

Okura A, Arakawa H, Oka H, Yoshinari T and Monden Y. Effect of genistein on topoisomerase activity and on the growth of [Val 12]Ha-ras-transformed NIH 3T3 cells. Biochem Biophys Res Commun 1988;157:183-189.

O'Neill ME, Carroll Y, Corridan B, Olmedilla B, Granado F, Blanco I, Van den Berg H, Hininger I, Rousell AM, Chopra M, Southon S and Thurnham DI. A European carotenoid database to assess carotenoid intakes and its use in a five-country comparative study. Br J Nutr 2001;85:499-507.

Opperman AM, Venter CS, Oosthuizen W, Thompson RL and Vorster HH. Meta-analysis of the health effects of using the glycaemic index in meal-planning. Br J Nutr 2004;92:367-381.

Osler M, Heitmann BL, Gerdes LU, Jorgensen LM and Schroll M. Dietary patterns and mortality in Danish men and women:a prospective observational study. Br J Nutr 2001;85:219-225.

Owen K and Hattersley AT. Maturity-onset diabetes of the young:from clinical description to molecular genetic characterization. Best Pract Res Clin Endocrinol Metab 2001;15:309-323.

Palmgren J and Kushi LH. Re:"Total energy intake:implications for epidemiologic analyses". Am J Epidemiol 1991;133:1291-1293.

Palozza P and Krinsky NI. Antioxidant effects of carotenoids in vivo and in vitro:an overview. Methods Enzymol 1992;213:403-420.

Pan DA, Lillioja S, Milner MR, Kriketos AD, Baur LA, Bogardus C and Storlien LH. Skeletal muscle membrane lipid composition is related to adiposity and insulin action. J Clin Invest1995;96:2802-2808.

Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH and Howard BV. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 1997;20:537-544.

Paolisso G and Giugliano D. Oxidative stress and insulin action:is there a relationship? Diabetologia 1996;39:357-363.

Paolisso G, Sgambato S, Pizza G, Passariello N, Varricchio M and D'Onofrio F. Improved insulin response and action by chronic magnesium administration in aged NIDDM subjects. Diabetes Care 1989;12:265-269.

Paolisso G, Sgambato S, Gambardella A, Pizza G, Tesauro P, Varricchio M and D'Onofrio F. Daily magnesium supplements improve glucose handling in elderly subjects. Am J Clin Nutr 1992;55:1161-1167.

Paolisso G, D`Amore A, Giugliano D, Ceriello A, Varicchio M and D`Onofrio F. Pharmacologic doses of vitamin E improve insulin action in healthy subjects and non-insulin dependent diabetic patients. Am J Clin Nutr 1993a;57:650-656.

Paolisso G, D'Amore A, Galzerano D, Balbi V, Giugliano D, Varricchio M and D'Onofrio F. Daily vitamin E supplements improve metabolic control but not insulin secretion in elderly type II diabetic patients. Diabetes Care 1993b;16:1433-1437.

Paolisso G, Di Maro G, Galzerano D, Cacciapuoti F, Varricchio G, Varricchio M and D'Onofrio F. Pharmacological doses of vitamin E and insulin action in elderly subjects. Am J Clin Nutr 1994a;59:1291-1296.

Paolisso G, Scheen A, Cozzolino D, Di Maro G, Varricchio M, D'Onofrio F and Lefebvre PJ. Changes in glucose turnover parameters and improvement of glucose oxidation after 4-week magnesium administration in elderly noninsulin-dependent (type II) diabetic patients. J Clin Endocrinol Metab 1994b;78:1510-1514.

Paolisso G, Gambardella A, Giugliano D, Galzerano D, Amato L, Volpe C, Balbi V, Varricchio M and D'Onofrio F. Chronic intake of pharmacological doses of vitamin E might be useful in the therapy of elderly patients with coronary heart disease. Am J Clin Nutr 1995;61:848-852.

Parillo M and Riccardi G. Diet composition and the risk of type 2 diabetes:epidemiological and clinical evidence. Br J Nutr 2004;92:7-19.

Parker DR, Weiss ST, Troisi R, Cassano PA, Vokonas PS and Landsberg L. Relationship of dietary saturated fatty acids and body habitus to serum insulin concentrations:the Normative Aging Study. Am J Clin Nutr 1993;58:129-136.

Pereira MA, Jacobs DJ, Slattery ML, Ruth KJ, Van Horn L, Hilner JE and Kushi LH. The Association of Whole Grain Intake and Fasting Insulin in Biracial Cohort of Young Adults:The CARDIA Study. CVD Prevention 1998;1:231-242.

Pereira MA, Jacobs DR, Jr., Pins JJ, Raatz SK, Gross MD, Slavin JL and Seaquist ER. Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. Am J Clin Nutr 2002;75:848-855.

Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH and Shaper AG. Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men. BMJ 1995;310:560-564.

Pietinen P, Nissinen A, Vartiainen E, Tuomilehto A, Uusitalo U, Ketola A, Moisio S and Puska P. Dietary changes in the North Karelia Project (1972-1982). Prev Med 1988;17:183-193.

Piironen V Tocopherols and tocotrienols in foods and in average Finnish diet (In Finnish with an English summary.). University of Helsinki, Department of food chemistry and technology, EKT:726. Helsinki, 1986

Pike MC, Bernstein L and Peters RK. Re:"Total energy intake:implications for epidemiologic analyses". Am J Epidemiol 1989;129:1312-1315.

Polidori MC, Mecocci P, Stahl W, Parente B, Cecchetti R, Cherubini A, Cao P, Sies H and Senin U. Plasma levels of lipophilic antioxidants in very old patients with type 2 diabetes. Diabetes Metab Res Rev 2000;16:15-19.

Pozzilli P and Di Mario U. Autoimmune diabetes not requiring insulin at diagnosis (latent autoimmune diabetes of the adult):definition, characterization, and potential prevention. Diabetes Care 2001;24:1460-1467.

Prior RL. Fruits and vegetables in the prevention of cellular oxidative damage. Am J Clin Nutr 2003;78:S570- S578.

Puhakainen I, Koivisto VA and Yki-Jarvinen H. Lipolysis and gluconeogenesis from glycerol are increased in patients with noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1992;75:789-794.

Pyörälä K, Laakso M and Uusitupa M. Diabetes and atherosclerosis:an epidemiologic view. Diabetes Metab Rev 1987;3:463-524.

Ramachandran K. Beta carotene metabolism in diabetes. Indian J Med Res 1973;61:1831-1834.

Rastas M, Seppänen R, Knuts L-R, Karvetti R-L and Varo P, eds. Ruoka-aineiden ravintosisältö. Nutrient composition of foods (In Finnish with English affiliations.). Social Incurance Institution. Helsinki, 1989.

Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595-1607.

Reunanen A. Tyypin 2 diabetes – uusi maailmanlaajuinen epidemia. Duodecim 2003;119:1409-1410.

Reunanen A. Suomalaisten diabetes:Harvinaisuudesta kansansairaudeksi. Diabetes ja lääkäri-lehti 2004;(6):6-11.

Reunanen A, Aromaa A, Pyörälä K, Punsar S, Maatela J and Knekt P. The Social insurance Institution's Coronary Heart Disease Study. Baseline Data and 5-Year Mortality Experience. Acta Med Scand Suppl 1983;673:1-120.

Reunanen A, Knekt P, Aaran RK and Aromaa A. Serum antioxidants and risk of non-insulin dependent diabetes mellitus. Eur J Clin Nutr 1998;52:89-93.

Reunanen A, Kangas T, Martikainen J and Klaukka T. Nationwide survey of comorbidity, use, and costs of all medications in Finnish diabetic individuals. Diabetes Care 2000;23:1265-1271.

Reunanen A, Kattainen A and the working group for cardiovascular diseases. Cardiovascular diseases and diabetes. In book:Aromaa A, Koskinen S, Eds. Health and Functional capacity in Finland. National Public Health Institute. Helsinki, 2004.

Rich-Edwards JW, Colditz GA, Stampfer MJ, Willett WC, Gillman MW, Hennekens CH, Speizer FE and Manson JE. Birthweight and the risk for type 2 diabetes mellitus in adult women. Ann Intern Med 1999;130:278-284.

Rimm EB, Manson JE, Stampfer MJ, Colditz GA, Willett WC, Rosner B, Hennekens CH and Speizer FE. Cigarette smoking and the risk of diabetes in women. Am J Public Health 1993;83:211-214.

Rimm EB, Chan J, Stampfer MJ, Colditz GA and Willett WC. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. BMJ 1995;310:555-559.

Rock CL, Jahnke MG, Gorenflo DW, Swartz RD and Messana JM. Racial group differences in plasma concentrations of antioxidant vitamins and carotenoids in hemodialysis patients. Am J Clin Nutr 1997;65:844-850.

Rudich A, Kozlovsky N, Potashnik R and Bashan N. Oxidant stress reduces insulin responsiveness in 3T3-L1 adipocytes. Am J Physiol Endocrinol Metab 1997;272:E935-E940.

Rösen P, Nawroth PP, King G, Moller W, Tritschler HJ and Packer L. The role of oxidative stress in the onset and progression of diabetes and its complications:a summary of a Congress Series sponsored by UNESCO-MCBN, the American Diabetes Association and the German Diabetes Society. Diabetes Metab Res Rev 2001;17:189-212.

Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL and Willett WC. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. JAMA 1997a;277:472-477.

Salmeron J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, Stampfer MJ, Wing AL and Willett WC. Dietary fiber, glycemic load, and risk of NIDDM in men. Diabetes Care 1997b;20:545-550.

Salmeron J, Hu FB, Manson JE, Stampfer MJ, Colditz GA, Rimm EB and Willett WC. Dietary fat intake and risk of type 2 diabetes in women. Am J Clin Nutr 2001;73:1019-1026.

Salonen JT, Nyyssönen K, Tuomainen T-P, Mäenpää PH, Korpela H, Kaplan GA, Lynch J, Helmrich SP and Salonen R. Increased risk of non-insulin dependent diabetes mellitus at low plasma vitamin E concentrations:a four year follow up study in men. Br Med J 1995;311:1124-1127.

Sanchez-Lugo L, Mayer-Davis EJ, Howard G, Selby JV, Ayad MF, Rewers M and Haffner S. Insulin sensitivity and intake of vitamins E and C in African American, Hispanic, and non-Hispanic white men and women:the Insulin Resistance and Atherosclerosis Study (IRAS). Am J Clin Nutr 1997;66:1224-1231.

Sargeant LA, Wareham NJ, Bingham S, Day NE, Luben RN, Oakes S, Welch A and Khaw KT. Vitamin C and hyperglycemia in the European Prospective Investigation into Cancer--Norfolk (EPIC-Norfolk) study:a population-based study. Diabetes Care 2000;23:726-732.

Sargeant LA, Khaw KT, Bingham S, Day NE, Luben RN, Oakes S, Welch A and Wareham NJ. Fruit and vegetable intake and population glycosylated haemoglobin levels:the EPIC-Norfolk Study. Eur J Clin Nutr 2001;55:342-348.

SAS/STAT User's Guide, version6. SAS Institute.Cary, NC, 1989

Sato Y, Hotta N, Sakamoto N, Matsuoka S, Ohishi N and Yagi K. Lipid peroxide level in plasma of diabetic patients. Biochem Med 1979;21:104-107.

Schulze MB, Liu S, Rimm EB, Manson JE, Willett WC and Hu FB. Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. Am J Clin Nutr 2004;80:348-356.

Shoff SM, Mares-Perlman JA, Cruickshanks KJ, Klein R, Klein BE and Ritter LL. Glycosylated hemoglobin concentrations and vitamin E, vitamin C, and beta-carotene intake in diabetic and nondiabetic older adults. Am J Clin Nutr 1993;58:412-416.

Simpson RW, Mann JI, Eaton J, Carter RD and Hockaday TD. High-carbohydrate diets and insulin-dependent diabetics. Br Med J 1979a;2:523-525.

Simpson RW, Mann JI, Eaton J, Moore RA, Carter R and Hockaday TD. Improved glucose control in maturity-onset diabetes treated with high-carbohydrate-modified fat diet. Br Med J 1979b;1:1753-1756.

Singh RB, Niaz MA, Rastogi SS, Bajaj S, Gaoli Z and Shoumin Z. Current zinc intake and risk of diabetes and coronary artery disease and factors associated with insulin resistance in rural and urban populations of North India. J Am Coll Nutr 1998;17:564-570.

Skarfors ET, Selinus KI and Lithell HO. Risk factors for developing non-insulin dependent diabetes:a 10 year follow up of men in Uppsala. BMJ 1991;303:755-760.

Slavin J. Whole grains and human health. Nutr Res Rev 2004;17:99-110.

Slavin JL, Martini MC, Jacobs DR, Jr. and Marquart L. Plausible mechanisms for the protectiveness of whole grains. Am J Clin Nutr 1999;70:459S-463S.

Slonim AE, Surber ML, Page DL, Sharp RA and Burr IM. Modification of chemically induced diabetes in rats by vitamin E. Supplementation minimizes and depletion enhances development of diabetes. J Clin Invest1983;71:1282-1288.

Snowdon DA and Phillips RL. Does a vegetarian diet reduce the occurrence of diabetes? Am J Public Health 1985;75:507-512.

Social Insurance Institution, Data in files 2003. Personal communication, Reunanen A, 2004.

Soman VR, Koivisto VA, Deibert D, Felig P and DeFronzo RA. Increased insulin sensitivity and insulin binding to monocytes after physical training. N Engl J Med 1979;301:1200-1204

Songer TJ and Zimmet PZ. Epidemiology of type II diabetes:an international perspective. Pharmacoeconomics 1995;8 Suppl 1:1-11.

Spiller GA, Chernoff MC, Hill RA, Gates JE, Nassar JJ and Shipley EA. Effect of purified cellulose, pectin, and a low-residue diet on fecal volatile fatty acids, transit time, and fecal weight in humans. Am J Clin Nutr 1980;33:754-759.

Stevens J, Ahn K, Juhaeri, Houston D, Steffan L and Couper D. Dietary fiber intake and glycemic index and incidence of diabetes in African-American and white adults:the ARIC study. Diabetes Care 2002;25:1715-1721.

Stolk RP, van Splunder IP, Schouten JS, Witteman JC, Hofman A and Grobbee DE. High blood pressure and the incidence of non-insulin dependent diabetes mellitus:findings in a 11.5 year follow-up study in The Netherlands. Eur J Epidemiol 1993;9:134-139.

Suarez A, Pulido N, Casla A, Casanova B, Arrieta FJ and Rovira A. Impaired tyrosine-kinase activity of muscle insulin receptors from hypomagnesaemic rats. Diabetologia 1995;38:1262-1270.

Tang X and Shay NF. Zinc has an insulin-like effect on glucose transport mediated by phosphoinositol-3-kinase and Akt in 3T3-L1 fibroblasts and adipocytes. J Nutr 2001;131:1414-1420.

Terry P, Hu FB, Hansen H and Wolk A. Prospective study of major dietary patterns and colorectal cancer risk in women. Am J Epidemiol 2001;154:1143-1149.

Trevisan M, Krogh V, Freudenheim J, Blake A, Muti P, Panico S, Farinaro E, Mancini M, Menotti A and Ricci G. Consumption of olive oil, butter, and vegetable oils and coronary heart disease risk factors. The Research Group ATS-RF2 of the Italian National Research Council. JAMA 1990;263:688-692.

Trowell HC. Letter:Dietary fibre hypothesis. Br Med J 1975;4:649.

Trowell H. Diabetes mellitus and dietary fiber of starchy foods. Am J Clin Nutr 1978;31:S53-S57.

Tuomi T, Carlsson Å, Li H, Isomaa B, Miettinen A, Nilsson A, Nissen M, Ehrnström BO, Forsén B, Snickars B, Lahti K, Forsblom C, Saloranta C, Taskinen MR and Groop LC. Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies. Diabetes 1999;48:150-157.

Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V and Uusitupa M. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343-1350.

Ursin G, Ziegler RG, Subar AF, Graubard BI, Haile RW and Hoover R. Dietary patterns associated with a low-fat diet in the national health examination follow-up study:identification of potential confounders for epidemiologic analyses. Am J Epidemiol 1993;137:916-927.

Uusitupa MI, Mykkanen L, Siitonen O, Laakso M, Sarlund H, Kolehmainen P, Rasanen T, Kumpulainen J and Pyörälä K. Chromium supplementation in impaired glucose tolerance of elderly:effects on blood glucose, plasma insulin, C-peptide and lipid levels. Br J Nutr 1992;68:209-216.

Uusitupa MI, Niskanen LK, Siitonen O, Voutilainen E and Pyörälä K. Ten-year cardiovascular mortality in relation to risk factors and abnormalities in lipoprotein composition in type 2 (non-insulin-dependent) diabetic and non-diabetic subjects. Diabetologia 1993;36:1175-1184.

Uzel N, Sivas A, Uysal M and Oz H. Erythrocyte lipid peroxidation and glutathione peroxidase activities in patients with diabetes mellitus. Horm Metab Res 1987;19:89-90.

Vahouny GV, Adamson I, Chalcarz W, Satchithanandam S, Muesing R, Klurfeld DM, Tepper SA, Sanghvi A and Kritchevsky D. Effects of casein and soy protein on hepatic and serum lipids and lipoprotein lipid distributions in the rat. Atherosclerosis 1985;56:127-137.

van Dam RM. The epidemiology of lifestyle and risk for type 2 diabetes. Eur J Epidemiol 2003;18:1115-1125.

van Dam RM, Rimm EB, Willett WC, Stampfer MJ and Hu FB. Dietary patterns and risk for type 2 diabetes mellitus in U.S. men. Ann Intern Med 2002a;136:201-209.

van Dam RM, Willett WC, Rimm EB, Stampfer MJ and Hu FB. Dietary fat and meat intake in relation to risk of type 2 diabetes in men. Diabetes Care 2002b;25:417-424.

van het Hof KH, Gartner C, Wiersma A, Tijburg LB and Weststrate JA. Comparison of the bioavailability of natural palm oil carotenoids and synthetic beta-carotene in humans. J Agric Food Chem 1999;47:1582-1586.

Varo P, Laine R, Veijalainen K, Pero K and Koivistoinen P. Dietary fibre and available carbohydrates in Finnish cereal products. J Agric Sci Finland 1984a;56:39-48.

Varo P, Veijalainen K, Espo A, Wetterhoff S and Koivistoinen P. Dietary fibre and carbohydrates in Finnish vegetables and fruits. J Agric Sci Finland 1984b;56:49-59.

Vatassery GT, Krezowski AM and Eckfeldt JH. Vitamin E concentrations in human blood plasma and platelets. Am J Clin Nutr 1983;37:1020-1024.

Venn BJ and Mann JI. Cereal grains, legumes and diabetes. Eur J Clin Nutr 2004;58:1443-1461.

Vessby B. Dietary fat and insulin action in humans. Br J Nutr 2000;83 Suppl 1:S91-96.

Vessby B, Aro A, Skarfors E, Berglund L, Salminen I and Lithell H. The risk to develop NIDDM is related to the fatty acid composition of the serum cholesterol esters. Diabetes 1994;43:1353-1357.

Vessby B, Unsitupa MI, Hermansen K, Riccardi G, Rivellese AA, Tapsell LC, Nalsen C, Berglund L, Louheranta A, Rasmussen BM, Calvert GD, Maffetone A, Pedersen E, Gustafsson IB and Storlien LH. Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women:The KANWU Study. Diabetologia 2001;44:312-319.

Vinik AI, Maser RE, Mitchell BD and Freeman R. Diabetic autonomic neuropathy. Diabetes Care 2003;26:1553-1579

Virtanen SM and Aro A. Dietary factors in the aetiology of diabetes. Ann Med 1994;26:469-478.

Vitelli LL, Folsom AR, Sharar E, Winkhart SP, Shimakawa T, Stevens J, Duncan BB and Champless LE. Association of dietary composition with fasting serum insulin level:The ARIC Study. Nutr Metab Cardiovasc Dis 1996;6:194-202.

Wagner JD, Cefalu WT, Anthony MS, Litwak KN, Zhang L and Clarkson TB. Dietary soy protein and estrogen replacement therapy improve cardiovascular risk factors and decrease aortic cholesteryl ester content in ovariectomized cynomolgus monkeys. Metabolism 1997;46:698-705.

Wang L, Folsom AR, Zheng ZJ, Pankow JS and Eckfeldt JH. Plasma fatty acid composition and incidence of diabetes in middle-aged adults:the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr 2003;78:91-98.

Wannamethee SG, Camargo CA, Jr., Manson JE, Willett WC and Rimm EB. Alcohol drinking patterns and risk of type 2 diabetes mellitus among younger women. Arch Intern Med 2003;163:1329-1336.

Ward WK, Beard JC, Halter JB, Pfeifer MA and Porte D, Jr. Pathophysiology of insulin secretion in non-insulin-dependent diabetes mellitus. Diabetes Care 1984;7:491-502.

Wei M, Gaskill SP, Haffner SM and Stern MP. Waist circumference as the best predictor of noninsulin dependent diabetes mellitus (NIDDM) compared to body mass index, waist/hip ratio and other anthropometric measurements in Mexican Americans--a 7-year prospective study. Obes Res 1997;5:16-23.

Weyer C, Bogardus C, Mott DM and Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest1999;104:787-794.

WHO. Diabetes mellitus:Report of a WHO study group. World Health Organization, Technical report series:727. Geneva, 1985.

WHO. Definition, Diagnosis and Classification of Diabetes Mellitus and its complications Part 1:Diagnosis and Classification of Diabetes Mellitus. World Health Organization, Department of Noncommunicable Disease Surveillance. Geneva, 1999.

Will JC and Byers T. Does diabetes mellitus increase the requirement for vitamin C? Nutr Rev 1996;54:193-202.

Will JC, Ford ES and Bowman BA. Serum vitamin C concentrations and diabetes:findings from the Third National Health and Nutrition Examination Survey, 1988-1994. Am J Clin Nutr 1999;70:49-52.

Willett W. Nutritional epidemiology. 2nd ed. Oxford University Press. New York, 1998.

Willett W and Stampfer MJ. Total energy intake:implications for epidemiologic analyses. Am J Epidemiol 1986;124:17-27.

Willett W, Manson J and Liu S. Glycemic index, glycemic load, and risk of type 2 diabetes. Am J Clin Nutr 2002;76:274S-280S.

Williams DE, Wareham NJ, Cox BD, Byrne CD, Hales CN and Day NE. Frequent salad vegetable consumption is associated with a reduction in the risk of diabetes mellitus. J Clin Epidemiol 1999;52:329-335.

Williams DE, Prevost AT, Whichelow MJ, Cox BD, Day NE and Wareham NJ. A cross-sectional study of dietary patterns with glucose intolerance and other features of the metabolic syndrome. Br J Nutr 2000;83:257-266.

Wirfält E, Hedblad B, Gullberg B, Mattisson I, Andren C, Rosander U, Janzon L and Berglund G. Food patterns and components of the metabolic syndrome in men and women:a cross-sectional study within the Malmo Diet and Cancer cohort. Am J Epidemiol 2001;154:1150-1159.

Wolever TM, Hamad S, Gittelsohn J, Gao J, Hanley AJ, Harris SB and Zinman B. Low dietary fiber and high protein intakes associated with newly diagnosed diabetes in a remote aboriginal community. Am J Clin Nutr 1997;66:1470-1474.

Würsch P and Pi-Sunyer FX. The role of viscous soluble fiber in the metabolic control of diabetes. A review with special emphasis on cereals rich in beta-glucan. Diabetes Care 1997;20:1774-1780.

Yang G, Shu XO, Jin F, Elasy T, Li HL, Li Q, Huang F, Zhang XL, Gao YT and Zheng W. Soyfood consumption and risk of glycosuria:a cross-sectional study within the Shanghai Women's Health Study. Eur J Clin Nutr 2004;58:615-620.

Ylönen K, Saloranta C, Kronberg-Kippilä C, Groop L, Aro A and Virtanen SM. Associations of dietary fiber with glucose metabolism in nondiabetic relatives of subjects with type 2 diabetes:the Botnia Dietary Study. Diabetes Care 2003a;26:1979-1985.

Ylönen K, Alfthan G, Groop L, Saloranta C, Aro A and Virtanen SM. Dietary intakes and plasma concentrations of carotenoids and tocopherols in relation to glucose metabolism in subjects at high risk of type 2 diabetes:the Botnia Dietary Study. Am J Clin Nutr 2003b;77:1434-1441.

Yoshinaga H and Kosaka K. Heterogeneous relationship of early insulin response and fasting insulin level with development of non-insulin-dependent diabetes mellitus in non-diabetic Japanese subjects with or without obesity. Diabetes Res Clin Pract 1999;44:129-136.

Zubay G. Integration of metabolism and hormone action. In book:Zubay G, Parson W, Vance D, Eds. Principles of biochemistry. WCB. Dubuque,1995.

Öhrvall M, Tengblad S and Vessby B. Lower tocopherol serum levels in subjects with abdominal adiposity. J Intern Med 1993;234:53-60.

APPENDIX TABLES

Appendix Table 1. Food grouping used in dietary pattern analyses

Food group	Food items
Processed meat	Canned meat, cured meat, salami, aspic, sausages, bacon
Red meat	Beef, pork, lamb, game, offal
Poultry	Chicken
Fish, canned or frozen	Canned tuna and -sardines, dried or frozen fish
Fish, salted or smoked	Smoked or salted sea and lake fish
Fish, unprocessed	Other than smoked or salted fish, shellfish
Eggs	Eggs
Butter	Butter
Margarine and oil	Margarines and oils
Whole milk	Whole milk
Regular dairy products	Cheese, cream, ice-cream, yoghurt
Reduced fat dairy products	Skimmed or low-fat milk, low fat cheese
Fruit	Pineapple, citrus fruit, peach, grapes and raisins, banana, plum, pear, cherry, and fruit juice
Berries	Cranberry, gooseberry, strawberry, black currant, red currant, lingonberry, cloudberry, raspberry
Yellow and red vegetables	Carrot, tomato, tomato sauce, paprika, mixed vegetables and vegetablejuice
Green vegetables	Cucumber, lettuce, spinach, parsley, cultivated leek, onions, cellery
Vegetables, other	Rutabaga, artichoke, swede, radish, cellery root, cauliflower, kohlrabi, pickled vegetables, and mushrooms
Peas and nuts	Peanuts, hazel nuts, almond, peas, beans and soy flour
Potato	Potato
Rye	Rye bread, rye crisp, rye flour
Wheat	Wheat flour, white bread, buns, pasta, grits
Other grain	Rice, rolled oats, barley groats, millet grains, buckwheat groats and flour
Jams and sugar rich condiments	Sweetened jams, marmalade, sugar, honey, cocoa

Appendix Table 2. Range of intake and relative risk[a] of type 2 diabetes (95% confidence interval) across the quartiles of the prudent dietary pattern scores and consumption of individual plant foods, total fiber and fiber components and antioxidant vitamins

	Quartile of intake				
Foods	1 (Lowest)	2	3	4 (Highest)	P-for trend
Prudent pattern score					
Relative risk	1	0.81 (0.61–1.08)	0.82 (0.62–1.10)	0.72 (0.53–0.97)	0.05
Vegetables, all, g/day[b]	<42	42–78	79–130	>130	
Relative risk	1	0.75 (0.56–1.00)	0.93 (0.70–1.22)	0.77 (0.57–1.03)	0.22
Yellow and red vegetables, g/day	<19	19–41	42–77	>77	
Relative risk	1	0.78 (0.59–1.04)	0.90 (0.68–1.18)	0.80 (0.60–1.06)	0.23
Green vegetables, g/day	<11	11–24	25–43	>43	
Relative risk	1	0.92 (0.71–1.21)	0.91 (0.69–(1.20)	0.69 (0.50–0.93)	0.02
Vegetables, other, g/day	<1	1–3	4–10	>10	
Relative risk	1	0.97 (0.73–1.30)	0.94 (0.71–1.24)	0.79 (0.58–1.07)	0.13
Potato, g/day	<132	132–196	197–283	>283	
Relative risk	1	1.09 (0.82–1.46)	1.27 (0.94–1.72)	1.42 (1.02–1.98)	0.03
Peas and nuts, g/day	<2	2–4	5–8	>8	
Relative risk	1	0.73 (0.55–0.95)	0.81 (0.61–1.07)	0.90 (0.67–1.20)	0.56
Fruit and berries, g/day	<33	33–83	84–156	>156	
Relative risk	1	0.77 (0.58–1.02)	0.83 (0.63–1.10)	0.69 (0.51–0.92)	0.03
Whole grain[c], g/day	<110	110–162	163–237	>237	
Relative risk	1	1.13 (0.86–1.48)	0.83 (0.61–1.12)	0.88 (0.63–1.23)	0.18

Total fiber, g/day	<19.3	19.3–25.3		25.4–33.1		>33.1		
Relative risk	1	0.76	(0.58–0.99)	0.69	(0.50–0.94)	0.66	(0.45–0.97)	0.02
Insoluble NCP[d], g/day	<8.8	8.8–12.0		12.1–16.5		>16.5		
Relative risk	1	0.75	(0.57–0.98)	0.76	(0.56–1.03)	0.67	(0.46–0.98)	0.04
Soluble fiber, g/day	<0.46	4.6–5.8		5.9–7.3		>7.4		
Relative risk	1	0.72	(0.55–0.95)	0.78	(0.58–1.06)	0.73	(0.50–1.05)	0.10
Cereal fiber, g/day	<12.1	12.1–17.3		17.4–24.4		>24.4		
Relative risk	1	0.81	(0.62–1.06)	0.76	(0.56–1.03)	0.69	(0.47–1.00)	0.04
Fruit fiber, g/day	<1.0	1.0–2.0		2.1–3.3		>3.3		
Relative risk	1	0.77	(0.57–1.03)	0.95	(0.72–1.26)	0.83	(0.62–1.13)	0.51
Vegetable fiber, g/day	<3.8	3.8–5.0		5.1–6.7		>6.7		
Relative risk	1	0.86	(0.65–1.14)	1.02	(0.77–1.37)	0.99	(0.72–1.37)	0.79
Vitamin E, mg/day[e]	<5.2	5.2–6.6		6.7–8.5		>8.5		
Relative risk	1	0.72	(0.54–0.96)	0.73	(0.53–1.00)	0.68	(0.47–1.00)	0.14
Vitamin C, mg/day	<50.0	50.0–68.8		68.9–92.3		>92.3		
Relative risk	1	0.73	(0.55–0.98)	0.85	(0.64–1.13)	0.85	(0.63–1.15)	0.75
Carotenoids, mg/day[f]	<1.9	1.9–2.9		3.0–4.7		>4.7		
Relative risk	1	0.74	(0.56–0.99)	1.00	(0.76–1.30)	0.69	(0.51–0.93)	0.14

[a]Adjusted for age, sex, body mass index, energy intake, smoking, geographical area, and family history of diabetes.
[b]Excluding potato.
[c] The whole grain food group contained rye bread, rye crisp bread, and all whole grain flours and other products (rye, whole wheat, wheat germ, rolled oats, barley, millet, buckwheat) derived from different grain foods (e.g., porridge, gruel, Karelian pie).
[d]Noncellulose polysaccharides.
[e]α-tocopherol equivalents.
[f]Sum of α-, β-, and γ-carotenes, lycopene, β-cryptoxanthin and lutein and zeaxanthin.